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CHRONIC FIBROCYSTIC DISEASE OF THE BREAST

HAROLD A. OBERMAN, M.D., and A. JAMES FRENCH, M.D., Ann Arbor, Michigan

ALTHOUGH many of the standard textbooks of pathology imply that adenofibroma, intraductal papilloma, and fibrocystic disease of the breast are separate and distinct entities, one has only to peruse a series of histopathologic preparations from these conditions to become aware of areas of coalescence. For this reason we reviewed 200 cases of benign breast disease, a term embracing the above 3 diagnoses, seen at The University of Michigan Medical Center over a 4 year period. Before discussing the findings of this study, a brief review of the salient pathologic features of these conditions is in order.

Fibrocystic disease is a term that embraces a multitude of histologic abnormalities, having a common denominator in an abnormal interplay between hormones, especially estrogen, and the parenchyma and stroma of the mammary gland. The condition has been known under a multitude of names, including chronic cystic mastitis, cystic disease, mastopathia cystica, and mammary dysplasia. In this condition a solitary mass may be felt in the breast or, more often, multiple nodules or a diffuse granularity may be present. Grossly, the tissue presents an irregular, gray-white, firm consistency. Frequently cysts of varying size are present. Microscopically one or all of the following may be present: ductal dilatation, apocrine metaplasia of ductal epithelium, intraductal proliferation of epithelium, adenosis, and interlobular and intralobular fibrosis. The ductal dilatation may be sufficiently extensive to form large cysts, the so-called blue-domed cyst of Bloodgood. The intraductal epithelial proliferation may be papillary or may involve the duct uniformly. Adenosis refers to a proliferation of terminal ductules (acinar type), or of small preterminal ducts (ductal type). Initially, in the former type, there is little stromal participation in this proliferation, giving the picture of florid adenosis. Later there is fibroblastic and myoepithelial cell proliferation which may eventually dominate the picture, giving rise to sclerosing or sclerosed adenosis. In the ductal type of adenosis, the often dilated small ducts are said to end blindly, giving rise to the term blunt-duct adenosis.

Adenofibroma usually presents as a firm, rubbery, freely movable, discrete mass in the breast. Upon removal from the breast it may appear encapsulated and have a gray-white cut surface, often with grossly visible slits or small cysts. Microscopically the tumor is nonencapsulated, the gross

From the Department of Pathology, The University of Michigan Medical Center, Ann Arbor.

TABLE I.—BENIGN BREAST DISEASE IN 200 PATIENTS

Diagnosis	*No. of cases*	*Age, years*	
		Range	*Average*
Fibrocystic disease	162	16–80	44
Gross cystic disease	104	22–80	44
Adenofibroma	79	16–58	34
Intraductal papilloma	16	38–89	53

TABLE II.—CLINICAL AND PATHOLOGIC FINDINGS IN 162 CASES OF FIBROCYSTIC DISEASE

	No. of cases	*Per cent of total*
Gross cysts	104	64
Microscopic findings		
Ductal dilatation	156	96
Apocrine change	142	87
Adenosis	56	35
Intraductal epithelial proliferation	63	39
Adenofibroma in same breast	46	28
Intraductal papilloma in same breast	13	8
Carcinoma in same breast	16	10
Development of carcinoma at later date	3	2
Reoperation for fibrocystic disease	40	25
History of menometrorrhagia	22	14

appearance of encapsulation being derived by compression of adjacent breast tissue. The dominant abnormality is a proliferation of connective tissue. In the young lesion this may be quite active, whereas in old adenofibromas the connective tissue may be hyalinized and even calcified. The distortion of ducts by the proliferating connective tissue may produce the intracanalicular growth pattern in which the ducts are elongated and compressed slitlike structures, or the pericanalicular growth pattern in which the ducts are not compressed by the proliferating connective tissue. More often there is a mixture of these growth patterns in any single lesion.

Intraductal papillomas are usually located in the subareolar ducts and frequently provoke bleeding or discharge from the nipple. Histologically the papilloma consists of a proliferation of epithelial elements supported by a connective tissue stalk. The involvement of the large lactiferous ducts is said by Haagensen to distinguish the intraductal papilloma from the papillomatosis frequently seen in fibrocystic disease.

It is of interest that many of these changes may also be manifested in the male breast. We have seen ductal dilatation with cyst formation, apocrine metaplasia of ductal epithelium, and intraductal papillomas associated with a bloody discharge in cases of gynecomastia.

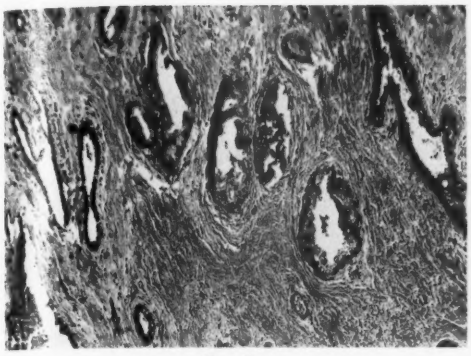
MATERIAL AND METHODS

Two hundred cases of benign breast disease—fibrocystic disease, adenofibroma, and intraductal papilloma—seen at The University of Michigan Medical Center between 1 July 1943 and 30 June 1945 and between 1 July 1952 and 30 June 1954 were arbitrarily selected from the files of the Department of Pathology. Cases of mammary duct ectasia and fat necrosis were excluded from the study. In each instance histologic material and paraffin blocks were available for review; frequently new sections were cut from the preserved blocks. From 3 to 17 sections were examined in each case. The routine stain was hematoxylin and eosin after fixation in 10 per cent formalin. The clinical record of each patient was reviewed. If additional operative procedures had been performed at an earlier or later date, this material was also reviewed.

RESULTS

Of the 200 patients with benign breast disease, 162 had histologic fibrocystic disease, 79 had adenofibromas, and 16 had intraductal papillomas (Table I). Obviously, more than one of these entities was present in several of the patients. Since some investigators consider the presence of gross cysts to be the chief factor in surgically recognizable fibrocystic disease, this group was also determined. The age incidence of these conditions is summarized in Table I. It will be noted that adenofibromas occurred in a distinctly younger age group than fibrocystic disease, and that intraductal papillomas were most prevalent in late menstrual and postmenopausal years.

Fibrocystic disease. The findings in the 162 patients with fibrocystic disease are summarized in Table II. It will be noted that ductal dilatation and apocrine metaplasia were the 2 most common components of



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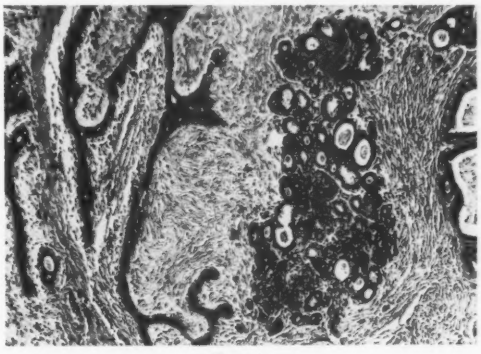

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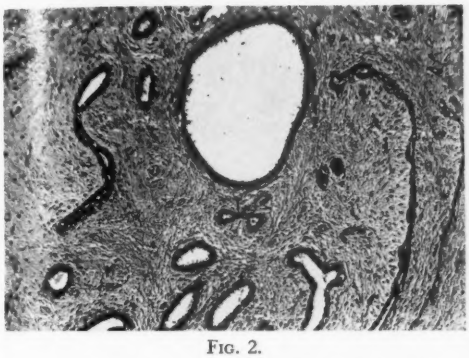

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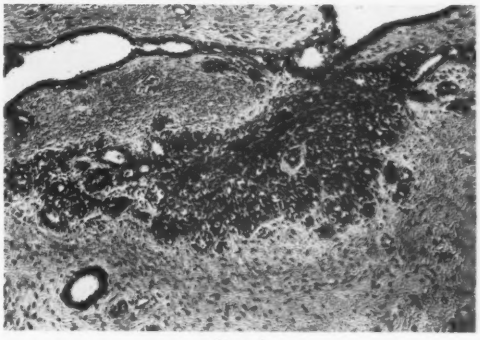


FIG. 4.

FIG. 1. Apocrine change in ductal epithelium in an adenofibroma. Hematoxylin and eosin, × 39.
FIG. 2. Dilated duct lined by hypertrophic epithelium in an adenofibroma. Hematoxylin and eosin, × 39.
FIG. 3. Proliferation of terminal ducts (adenosis) in adenofibroma. Hematoxylin and eosin, × 39.
FIG. 4. Florid adenosis in an adenofibroma. Hematoxylin and eosin, × 39.

this histologic complex. Adenosis usually occurred in small foci and only rarely dominated the histologic picture. This is in keeping with prior studies by Sandison on this subject. Likewise, intraductal epithelial proliferation was present in 63 cases but was extensive in only a minority of these. Grossly visible cysts, greater than 1 millimeter in diameter, occurred in 104 cases. Twenty-three of the latter patients were postmenopausal.

Adenofibromas were present elsewhere in the breast in 46 patients with fibrocystic disease, whereas intraductal papillomas occurred in 13 cases. In 40 instances the patient had had a prior operation, or required operation at a future date, for either fibrocystic disease or adenofibroma. Of the patients with gross cysts, 19 had concomitant adenofibromas.

Carcinoma subsequently developed in only 3 of these patients. In the instances of simultaneous fibrocystic disease and carcinoma, the fibrocystic disease probably is only an incidental finding.

Subsequent to reports by Martel and Sommers and Nathanson of the association of fibrocystic disease with ovarian and adrenal abnormalities, we reviewed the menstrual histories of these patients. In 22 instances a history of profuse menstrual bleeding or of intermenstrual bleeding was obtained; in most cases this had been severe enough to require curettage or hysterectomy.

TABLE III.—CLINICAL AND PATHOLOGIC FINDINGS IN 79 CASES OF ADENOFIBROMA

	No. of cases	*Per cent of total*
Fibrocystic disease elsewhere in breast	46	58
Gross cystic disease elsewhere in breast	19	24
Fibrocystic disease in adenofibroma	35	48
Apocrine change	28	35
Adenosis	6	7
Intraductal epithelial proliferation	17	22
Intraductal papilloma in same breast	2	3
Development of new adenofibromas	4	5
Multiple adenofibromas	15	19
Carcinoma in same breast	3	4
Development of carcinoma at later date	1	1
History of menometrorrhagia	9	11

TABLE IV.—CLINICAL AND PATHOLOGIC FINDINGS IN 16 CASES OF INTRADUCTAL PAPILLOMA

	No. of cases
Fibrocystic disease elsewhere in breast	13
Bleeding from nipple*	13
Carcinoma in same breast	1
Postmenopausal*	8
Apocrine change in papilloma	10
History of menometrorrhagia	4

*Data not availble on 1 patient.

Adenofibroma. As noted in Table I, the adenofibromas occurred in a distinctly younger age group than did fibrocystic disease or intraductal papillomas. In 4 of the patients additional adenofibromas requiring excision developed, and in 1 patient carcinoma was found at a later date. One patient had 3 operations for removal of adenofibromas over a 7 year period.

Of primary interest is the occurrence of manifestations of fibrocystic disease within 35 of the adenofibromas. This consisted of apocrine metaplasia of epithelium, adenosis, or intraductal epithelial proliferation; usually more than one of these findings was present (Figs. 1 to 6). In 46 cases fibrocystic disease was present elsewhere in the breast (Fig. 7).

Architecturally the majority of adenofibromas had a mixed intracanalicular and pericanalicular growth pattern. Menstrual history was also reviewed in these patients, and 9 were found to have a history of abnormal menstrual flow. The findings in these patients are summarized in Table III.

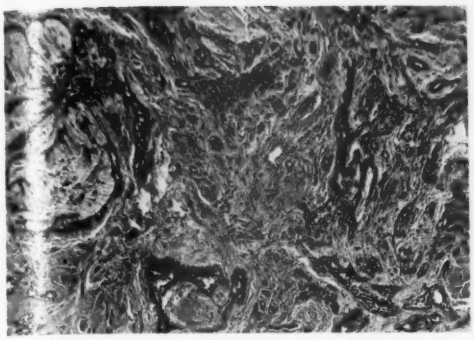
Intraductal papilloma. Of the 16 patients with intraductal papillomas, 8 were postmenopausal, and a sanguineous discharge from the nipple was present in 13. The findings in these cases are summarized in Table IV. Apocrine metaplasia of the epithelium of the papilloma was present in 10 cases (Fig. 8), and fibrocystic disease was present elsewhere in the breast in 13 cases. Concomitant occurrence of fibrocystic disease, adenofibroma, and intraductal papilloma was present in 2 cases. A history of prior hypermenorrhea or of intermenstrual bleeding was present in 4 cases.

DISCUSSION

Although the majority consider fibrocystic disease, adenofibroma, and intraductal papilloma as distinct entities, contrasting viewpoints may be found in the literature. In their treatise on the breast, Cheatle and Cutler regarded adenofibromas as benign connective tissue tumors, similar to lipomas. Foote and Stewart considered adenofibromas as proliferative lesions, but of a different order from other mammary proliferations. In his lengthy monograph, Semb vacillated between these viewpoints, at one time claiming that circumscribed fibroadenomas could be formed on the basis of fibroadenomatosis cystica (fibrocystic disease) and at another point claiming that there is no connection between the 2 entities. At the conclusion of their study of 225 breasts, Frantz and her co-workers expressed uncertainty as to whether adenofibromas have as little relationship to chronic cystic disease as they had originally supposed.

Rodman (11, 12), and Ingleby concluded that adenofibromas, chronic cystic disease, and intraductal papillomas were variations of the same basic disease process. Similarly, Oliver and Major noted interrelationships between fibrocystic disease and adenofibromas.

From the foregoing, it is evident that fibrocystic disease, intraductal papilloma, and adenofibroma are closely related entities. Although they have dissimilar age incidences, and also appear relatively dis-



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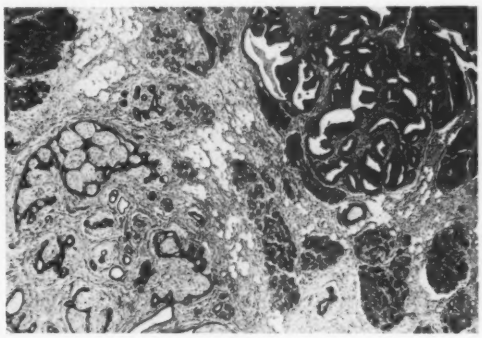

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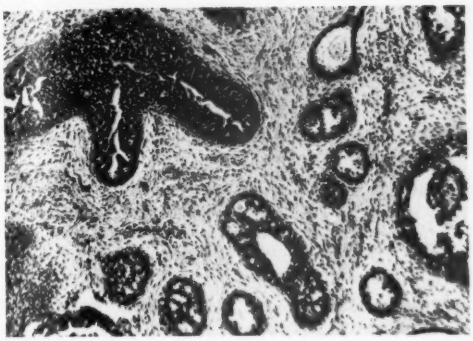

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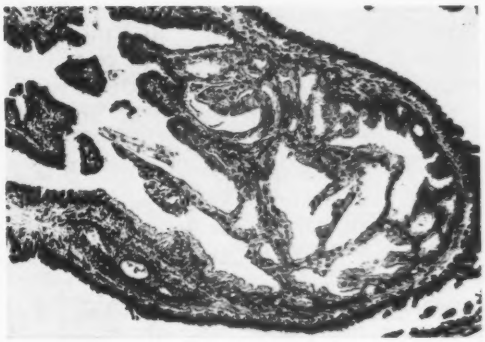

FIG. 8.

FIG. 5. Sclerosing adenosis in an adenofibroma. Hematoxylin and eosin, × 39.
FIG. 6. Proliferation of ductal epithelium in an adenofibroma. Hematoxylin and eosin, × 39.
FIG. 7. Ductal type of adenosis, right, adjacent to small adenofibroma, left. Hematoxylin and eosin, × 14.
FIG. 8. Apocrine change in epithelium in an intraductal papilloma. Hematoxylin and eosin, × 92.

tinct clinically, there is considerable clinical, gross, and histopathologic overlap. This fact is exemplified by the presence of elements of fibrocystic disease, such as apocrine metaplasia or adenosis, within adenofibromas and intraductal papillomas. It has also been substantiated by the simultaneous occurrence of 2 or all 3 of these conditions in the same breast. Since this study was based on operative specimens, in some instances only scant mammary tissue adjacent to the adenofibroma or intraductal papilloma was available for examination. Consequently, the frequency of concomitant occurrence of these lesions within this series may be somewhat low.

These conditions appear to have their genesis in an abnormal response of the mammary stroma and parenchyma to hormonal stimulus. One may postulate that in the younger woman the response is chiefly stromal, while in the older patient it is principally epithelial. As a result of continuation of this abnormal hormonal end-organ response, recurrence of the mammary disease would be anticipated and is borne out by the reported findings. The 25 per cent reoperation rate of fibrocystic disease in this series is somewhat higher than that reported by Davis and Simons.

The hormonal basis for benign breast disease is substantiated by animal studies

in which administration of estrogens has produced ductal dilatation, proliferation, and other changes seen in these conditions. The role of progesterone in influencing the mammary stroma and parenchyma is uncertain.

Because of the small number of cases surveyed, a statistical analysis of these results is not feasible.

SUMMARY

Two hundred cases of benign breast disease, namely, fibrocystic disease, adenofibroma, and intraductal papilloma, have been reviewed clinically and histopathologically. The frequent occurrence of manifestations of fibrocystic disease of the breast, such as apocrine metaplasia or adenosis, within adenofibromas and intraductal papillomas has been noted. Likewise, the frequent concomitant occurrence of these conditions in the same breast has been cited. Also reviewed is the frequency of recurrence of mammary disease in these patients.

Adenofibromas, fibrocystic disease, and intraductal papillomas do not appear to represent distinct disease entities, but rather form a spectrum of conditions having their basis in an abnormality between hormonal stimulus to the breast, principally estrogen, and stromal and epithelial response. Therefore, we suggest expanding the connotation of the designation fibrocystic disease to include this complex of lesions of the mammary gland.

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ANTITHYROID DRUGS IN THE TREATMENT OF HYPERTHYROIDISM

JOHN C. McCLINTOCK, M.D., F.A.C.S., Albany, New York,
FRANK X. GASSNER, Ph.D., Fort Collins, Colorado,
NEWTON BIGELOW, M.D., Teaneck, New Jersey, and
WILLIAM A. BAKER, M.D., Keewatin, Ontario, Canada

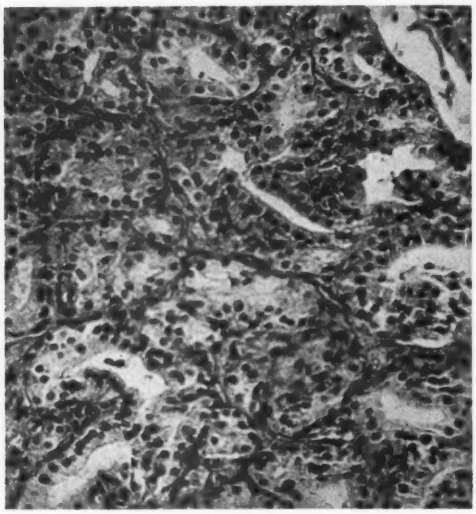
THE PLACE of antithyroid drugs in the management of thyrotoxicosis has undergone considerable change since Astwood first introduced thiouracil. There is no doubt that these compounds have reduced the morbidity and mortality attending thyroidectomy, and, for some patients, antithyroid drug therapy has eliminated the need for thyroid surgery. Differences of opinion regarding the drug of choice do exist, and there are practical considerations that make one compound superior to others in certain situations. This study was undertaken to review our experience of nearly 15 years with 3 of these drugs in the treatment of 843 patients. Until last year, we were denied the use of carbimazole, so widely used in the United Kingdom, so we are reporting on results obtained with propylthiouracil, tapazole (1-methyl-2-mercaptoimidazole), and itrumil (5-iodo-2-thiouracil, sodium salt).

Regardless of the efficacy of antithyroid drugs in the management of hyperthyroidism certain criteria must be met when considering them as the only form of treatment for this disease. In order to claim a medical remission, it is necessary that (a) the patient remain free from symptoms of toxic goiter after withdrawal of the drug and (b) there be only slight or no enlargement of the thyroid gland due to use of the drug. These restrictions on a medically produced cure decrease the percentage of such cures well below that accepted by many internists. On these terms we were able to obtain a medical cure of toxic diffuse goiter in 14 per cent (17 of 120) of the patients treated with propylthiouracil, 15 per cent (25 of 164) of those receiving tapazole, and 11 per cent (61 of 559) of those given itrumil. To achieve these results the patients received the drug for 12 to 36 months with an optimum therapeutic time of 18 months. It is only fair to say that itrumil has become the drug of choice for preoperative preparation of patients by one of us (J.C.M.) and that, for most clinicians today, antithyroid compounds find their greatest usefulness in such preparation for thyroidectomy.

All compounds had toxic manifestations. Fatal agranulocytosis developed in 1 patient given propylthiouracil (2). Three patients on this regimen suffered granulocytopenia to a degree that warranted hospitalization and vigorous therapy. Agranulocytosis responded successfully to the usual therapeutic measures in 1 patient receiving tapazole. Hives, skin rash, drug fever, nausea, or arthralgia occurred with all drugs as illustrated in Table I. Itrumil showed the lowest toxic symptoms (4.9 per cent), while tapazole and propylthiouracil produced 6.1 and 8.2 per cent respectively. Since this report was first written and the tables pre-

TABLE I.—TOXIC REACTIONS DURING TREATMENT WITH ANTITHYROID DRUGS

	Propylthiouracil		*Tapazole*		*Itrumil*	
Reaction	*No.*	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*
Urticaria	0	0	1	0.6	0	0
Hives	1	0.8	6	3.7	2	0.4
Skin rash	4	3.3	0	0	4	0.8
Drug fever	0	0	0	0	8	1.6
Nausea	1	0.8	1	0.6	7	1.2
Arthralgia	0	0	1	0.6	5	0.9
Granulocytopenia	3	2.5	0	0	0	0
Agranulocytosis	1	0.8	1	0.6	0	0
Totals	10	8.2	10	6.1	26	4.9



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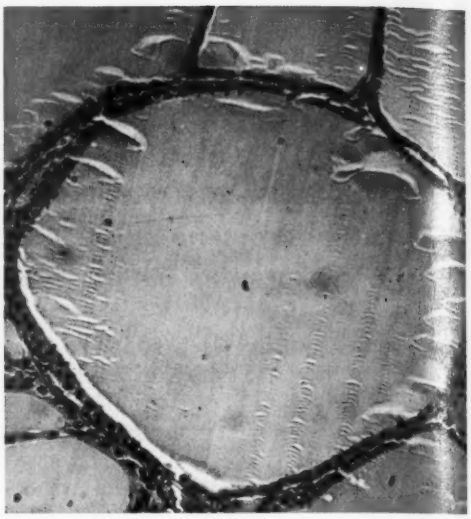


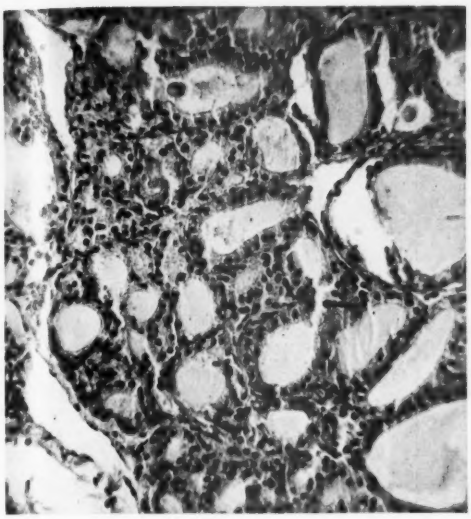
FIG. 2.

FIG. 1. Pretreatment biopsy in a case of acute hyperthyroidism.
FIG. 2. Section from posttreatment thyroidectomy specimen in same case as Figure 1.

pared, an instance of nonfatal agranulocytosis has been observed while the patient was receiving itrumil. Daily dose levels have been as high as 1,000 milligrams for itrumil and propylthiouracil with the majority of patients receiving 400 to 600 milligrams per day. Doses of tapazole ranged between 40 and 60 milligrams per day with the highest dose 80 milligrams daily. With the exception of patients receiving dose levels of 800 to 1,000 milligrams per day of itrumil or propylthiouracil, this series of patients has been treated on an outpatient basis.

It has previously been observed by McClintock and Lyons that resumption of interrupted therapy or increasing the dosage of propylthiouracil during treatment frequently resulted in the development of granulocytopenia. Catz (4) has shown that the use of phenobarbital concurrently with itrumil increased the frequency of skin rashes. Burrell and associates summarized the literature regarding toxic reactions and added their experience with carbimazole. They reported toxic manifestations in 2 per cent of their patients receiving carbimazole and added that 1 case of fatal bone aplasia developed during therapy.

From the foregoing it appears reasonable to conclude that itrumil has advantages over the other compounds with the possible exception of carbimazole. This is certainly true in the preoperative preparation of hyperthyroid patients. Because itrumil contains iodine as part of its molecular configuration there is no necessity for the administration of iodides in the final 2 to 3 week preoperative period. This inclusion of iodine creates one restriction which prohibits the use of itrumil if any consideration of using radioactive iodine is entertained. It was observed very early in clinical investigation with itrumil that the thyroid glands prepared by it were more easily resected and were less friable and vascular than those prepared by other drugs plus iodide. Furthermore, experience eventually dictated that resection of the thyroid gland had to be less radical after preparation by itrumil if postoperative hypothyroidism was to be avoided. This experience plus observation of the marked involution obtained when



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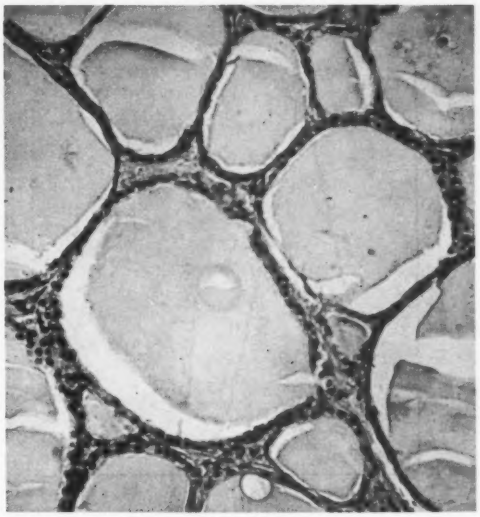


FIG. 4.

FIG. 3. Pretreatment biopsy in a case of chronic hyperthyroidism.
FIG. 4. Section from posttreatment thyroidectomy specimen in same case as Figure 3.

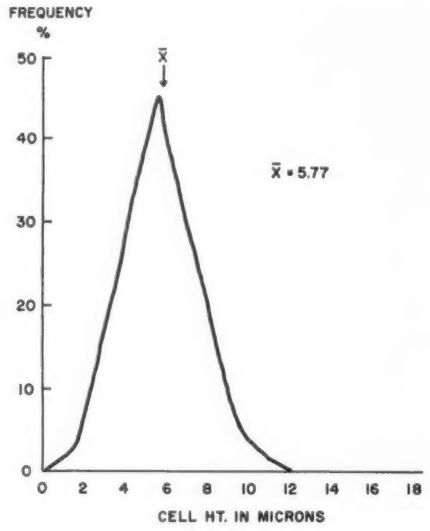
pretreatment thyroid gland biopsy specimens were compared with posttreatment specimens allowed more critical comparison of thyroid tissues prepared for surgical resection by various antithyroid drugs.

Thyroid tissues were obtained in a few selected cases by biopsy before drug therapy and again after treatment and surgical resection. Glands prepared only by Lugol's solution were from patients who had been operated upon prior to initiation of this clinical trial with antithyroid agents. Normal tissues were obtained at autopsy from patients of comparable age who were free of disease that could possibly affect the thyroid gland. Resected tissue was weighed and a sample removed for assay of iodine; the remaining tissue was fixed in Bouin's fluid, sectioned, and stained according to the method of Gassner and associates.

The normal thyroid gland is composed of many acini filled with colloid and lined with low cuboidal epithelial cells. The thyroid biopsy specimens of acute and chronic diffuse hyperthyroidism obtained before treatments show certain histologic changes such as loss of colloid and increase in epithelial cell height. In the acute disease, the biopsy shows that almost all colloid has been lost and the epithelial cells have increased in height from low cuboidal to columnar in type, demonstrating the hyperplasia characteristic of the disease. In the chronic disease, the colloid loss and cellular changes are evident, but not as marked. In both instances, after itrumil therapy, the histologic picture reverted to that of a normal gland with colloid replacement and regression of epithelium cell height to low cuboidal type.

The appearance of thyroid tissue from a patient with acute hyperthyroidism is shown in Figure 1.

The patient was 25 years old with symptoms of hyperthyroidism of 1 month's duration. The diagnosis was acute toxic diffuse goiter. The basal metabolic rate was plus 31 per cent; blood cholesterol level was 185 milligrams per cent. Thyroid biopsy was performed. With itrumil therapy, 600 milligrams daily, for 7 weeks, the pulse rate decreased from 124 to 80; weight increased from 156 to 162 pounds; the basal metabolic rate and cholesterol returned to normal levels. The gland did not enlarge and became firmer to palpation; thyrotoxic symptoms were con-



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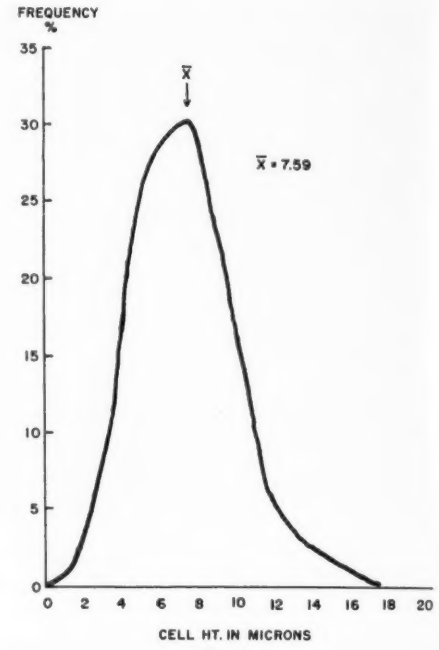

FIG. 6.

FIG. 5. Frequency distribution of thyroid cell heights from 2,114 measurements in controls.

FIG. 6. Frequency distribution of thyroid cell heights from 1,963 measurements in patients treated with Lugol's solution only.

trolled; subtotal thyroidectomy was performed with ease and little vascularity was noted. The appearance of the gland after itrumil is shown in Figure 2.

Figure 3 depicts a patient with chronic hyperthyroidism.

The patient was a 51 year old female, with symptoms of mild hyperthyroidism of over 1 year's duration, associated with a 30 pound weight loss, hyperexcitability, and nervousness, with an initial basal metabolic rate of plus 67 per cent. Therapy consisted of 400 milligrams of itrumil daily. Marked symptomatic improvement and a 10 pound weight gain occurred during the following 2 months of treatment. The pulse rate was reduced from 104 to 76 and the basal metabolic rate became normal. Subtotal thyroidectomy was performed. The gland was well involuted, relatively avascular, and easily removed (Fig. 4).

Protein bound iodine content of the blood was determined before, during, and after treatment with the various antithyroid drugs. Similarly, the concentration of thyroid iodine in surgical specimens was determined. These data will be the subject of a separate report, but it should be pointed out here that protein bound iodine values of as high as 800 micrograms per cent were recorded during treatment. Even butanol extractable iodine values may be abnormally high for more than 6 weeks after cessation of itrumil therapy.

Since one of the major criteria to denote regression of hyperthyroidism with normalization of the thyroid tissue is reduction in epithelial hypertrophy, the acinar cell heights were measured. The thyroid gland acini in 5 areas of each microscopic slide of stained tissue were projected in a darkened room through a prism ocular onto white paper where they were outlined and measured later at leisure in good light. Projection distance and magnification were adjusted (×500) to permit measurement of height directly in microns, e.g. 2 microns equal 1 millimeter. This method was a modification of that by Hardy. Five autopsy specimens and 1 surgical specimen were reviewed as normal. The thyroid glands from 15 patients prepared with tapazole and a

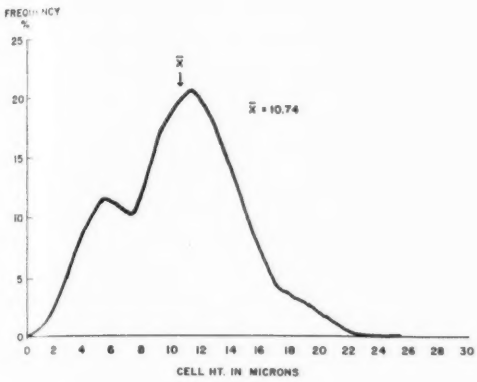

FIG. 7.

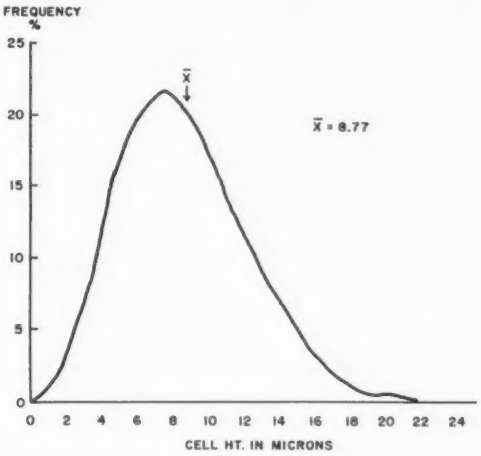

FIG. 9.

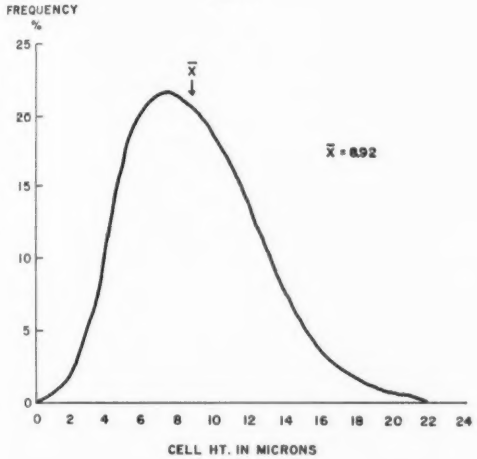

FIG. 8.

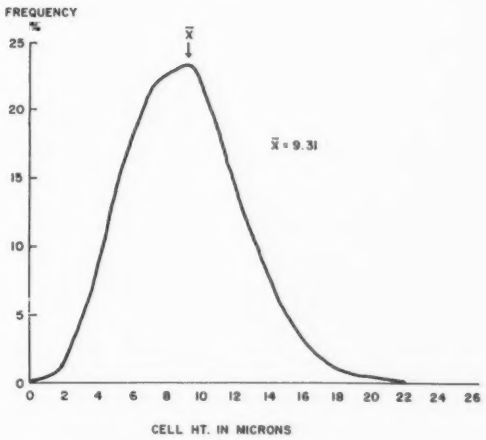

FIG. 10

FIG. 7. Frequency distribution of thyroid cell heights from 1,565 measurements in patients treated with propylthiouracil and Lugol's solution.

FIG. 8. Frequency distribution of thyroid cell heights from 2,746 measurements in patients treated with propylthiouracil followed by Lugol's solution.

FIG. 9. Frequency distribution of thyroid cell heights from 7,254 measurements in patients treated with itrumil.

FIG. 10. Frequency distribution of thyroid cell heights from 7,792 measurements in patients treated with tapazole followed by Lugol's solution.

like number of itrumil treated glands were studied. In 11 patients treated with propylthiouracil and iodide or propyl followed by iodide thyroid glands were examined and compared with glands from patients treated during the years when preparation was by iodide alone.

The acinar cell height data were arranged in a frequency distribution for each type of treatment by using classes of 2 microns in cell height. Curves were drawn using the midpoints of each type. The curves (Figs. 5 to 10) were smooth with the exception of that of thiouracil and Lugol's together. The

TABLE II.—THYROID CELL HEIGHT MEASUREMENTS

Treatment of patients	*No. of measurements*	*Aver. cell height, microns*	*S.E. ± —*	*Sign. diff.— From normal control*	*Sign. diff.— From itrumil treated*
Normal control—None	2114	5.767	.036	—	**
Lugol's solution only	1963	7.590	.060	**	**
Itrumil	7254	8.774	.045	**	—
Propylthiouracil +Lugol's	1565	10.736	.108	**	**
Popylthiouracil followed by Lugol's	2746	8.915	.071	**	NS
Tapazole followed by Lugol's	7792	9.309	.039	**	**

**P= <0.01.

mean cell heights and their standard errors were determined by using large sample formulas. Differences between means were compared by Student's "t" test. Table II summarizes the results of these calculations. Catz and associates (5) have reported cell height measurements in a small series of itrumil prepared thyroid glands. In 10 of 15 patients average acinar cell height was less than 10 microns; in 1, mean height was 11.2 microns, and in 4 other patients the average height was above 11.6 microns. They concluded that itrumil showed effective antithyroid action and no goitrogenicity.

Sarcione and Barrett investigated the antithyroid activity of 5-iodo-2-thiouracil in rats and found it to be an active antithyroid agent. They compared this drug with the thiouracil-iodide combinations and showed that it was less goitrogenic and less depressant to thyroid iodine levels. They concluded that the antithyroid effect of the compound was strongly modified by the release of iodide from the drug even though the quantity of iodide released amounted to only about 20 per cent of the drug injected. They also found that a mixture of thiouracil and iodine increased the thyrotropin activity of the pituitary while the iodinated thiouracil did not.

SUMMARY

The clinical experience with antithyroid drugs involving 843 patients and under the direction of one physician is presented. All antithyroid agents were associated with toxic reactions. Reactions occurring during itrumil therapy were less frequent than those observed in patients given thiouracil, propylthiouracil, and tapazole. Measurements of thyroid gland acinar cell heights indicate that itrumil produces good involution which is borne out by production of less friable and less vascular thyroid tissue on which to operate. We wish to emphasize this feature as being of great importance to the surgeon. Experimental studies confirm that the compound has excellent antithyroid properties which are different in many respects from other drugs because of low goitrogenicity.

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CLINICAL SIGNIFICANCE OF THE SPERMATIC GRANULOMA

EDWARD M. MAHONEY, M.D., Brookline, Massachusetts

SPERMATIC GRANULOMA is a benign but distressing lesion. It is clinically significant because it mimics other lesions of the epididymis and masquerades under other diagnoses. The demonstration of 2 spermatic granulomas in a study of 50 routine autopsies by Sundarasivarao and of 5 in 350 by Glassy and Mostofi suggests that the true incidence of spermatic granuloma far exceeds that implied by the relatively few cases reported. This is not surprising in view of the 87 cases in the literature which note the stated clinical preoperative or preautopsy diagnosis to have been undetermined or in error in all but a few cases. The clinical findings and associated high incidence of genitourinary tract infection make readily understandable the difficulty in differentiating this lesion from recurrent bacterial epididymitis. The present report adds to the literature 3 cases which illustrate the pathogenetic role of infection and of genital tract obstruction and the importance of correct diagnosis in the care of patients with spermatic granuloma.

PATHOGENESIS

The prerequisite for the formation of a spermatic granuloma is the escape of spermatozoa from their normal intratubular habitat into interstitial tissue. A sterile inflammatory reaction ensues which produces a granuloma with specific pathologic characteristics. Reconstruction of the pathogenesis by histologic study of the lesion has led to a difference of opinion as to whether damage of the epithelium and basement membrane from inflammation or increased intratubular pressure due to obstruction is the primary etiologic mechanism. The basis for this apparent conflict has been the demonstration of a predominance of inflammatory changes in some series and of tubular dilatation in others. A review of the cases now reported indicates that each of these primary mechanisms, alone or in combination, may operate in the formation of spermatic granuloma.

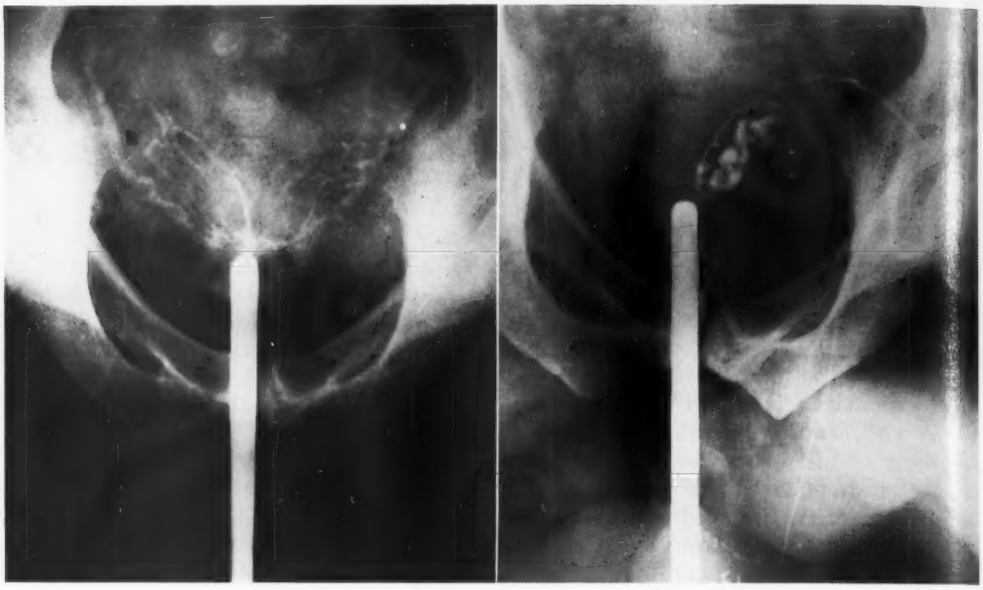
Fifty-one of 87 cases in the literature have been associated with previous infection, trauma, or obstruction of the genitourinary tract. The remaining 36 comprise for the most part those discovered incidentally at operation or postmortem examination, or those in patients presenting an inadequate recorded history.

Acute inflammation due to infection may set the stage for granuloma formation both by direct tubular wall damage and by the natural sequel of fibrosis, cicatrization, and stricture formation in the genital tract. Patient 1 of the present report demonstrates a spermatic granuloma associated with ipsilateral obstruction of the vas deferens arising from repeated infection. Those cases of Friedman and Russell and their associates occurring secondary to vasectomy and Friedman's Case 10 with bilateral vas deferens and seminal vesicular hypoplasia indicate that obstruction of the genital tract alone can be of etiologic significance. The role of tubular rupture by direct trauma in association with granuloma formation was present in 9 patients recorded in the literature.

DIAGNOSIS

The majority of patients with spermatic granuloma are in the age group of greatest potency and suffer from pain and swelling

From the Urology Section of the Surgical Service, Veterans Administration Hospital, West Roxbury, Massachusetts.



a b

FIG. 1. Bilateral retrograde vasography demonstrating obstruction of the right vas deferens, and normal architecture and patency of the left vas deferens down to and including the convoluted epididymal tubules.

of the epididymis. Lack of fever and absent or moderate leukocytosis are consistent with the sterile nature of this inflammatory process and are helpful in its differentiation from acute bacterial epididymitis. A history of previous acid-fast bacillus or routine bacterial genitourinary tract infection understandably predisposes not only to the likelihood of recurrent bacterial infection but also to spermatic granuloma formation. A favorable response to conservative therapy, as in Patient 1, may occur and serve to delay or obscure the diagnosis. Negative bacteriologic studies coupled with suspicion of tumor present a diagnostic problem which may warrant retrograde vasography and exploration of the involved epididymis. Ipsilateral obstruction of the vas deferens, as demonstrated by retrograde vasography, favors the diagnosis of spermatic granuloma. In the reported cases, definitive diagnosis has depended on pathologic examination of the lesion.

REPORTS OF PATIENTS

PATIENT 1. A 31 year old single, white fruit peddler entered with a chief complaint of pain in the right testicle of 7 months' duration. Six months prior to admission, the right testicle had enlarged to 3 times its normal size and had become tender. He was treated with sitz baths, and the testicle decreased to normal size. Subsequently, ejaculation was associated with immediate sharp pain in the right groin and right testicular swelling which persisted from 1 to 3 days. Regression occurred spontaneously without the use of antibiotics, and at no time was there an associated febrile reaction.

His past history revealed multiple instances of gonorrheal urethritis and was negative for tuberculosis and syphilis. Physical examination was not remarkable except for a nontender, firm, globular enlargement of the lower pole of the right epididymis.

Laboratory studies revealed no pyuria and a sterile urine. Serologic reaction for syphilis was negative. The white blood cell count was 8,100 with a normal differential.

Bilateral retrograde vasography demonstrated an obstruction in the proximal right vas deferens and seminal vesicle; the left vas deferens and seminal vesicle were patent, with filling down to the left epididymis (Fig. 1). A right epididymectomy was per-

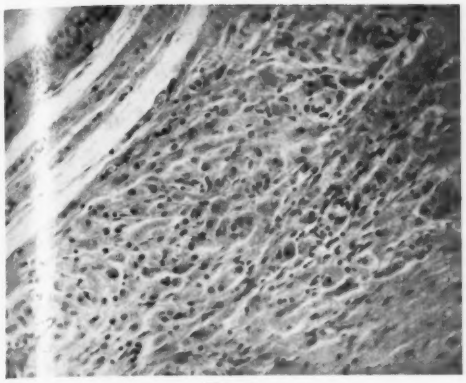


FIG. 2.

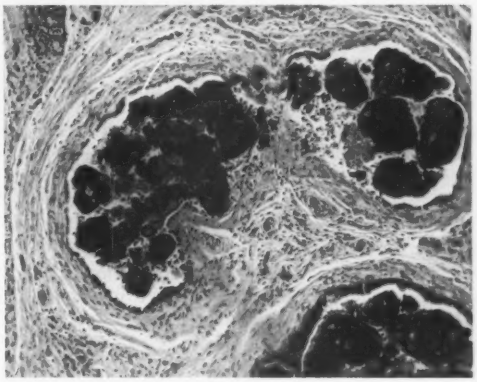


FIG. 3.

FIG. 2. Section of epididymis from Patient 2 showing extensive macrophage infiltration of stroma adjacent to an epididymal tubule.

FIG. 3. Section from Patient 3. Observe the tubules distended with agglutinated masses of sperm and containing focal deposition of calcium. The epithelial lining of the tubule is interrupted, and the contents of the tubule are being spilled into the peritubular tissue.

formed, and the nodule of the lower pole of the epididymis was demonstrated to be a spermatic granuloma.

The role of genital tract obstruction in the etiology of spermatic granuloma was suggested by the onset of pain and swelling of the epididymis subsequent to ejaculation and was demonstrated roentgenographically by retrograde vasography.

PATIENT 2. A 43 year old painter was hospitalized for the third time for re-evaluation of presumable tuberculosis of the genitourinary tract. One year earlier a 24 hour episode of pain in the left testis, associated with fever to 101 degrees, brought the patient to the hospital where he was treated with bed rest, scrotal elevation, ice pack, and antibiotic therapy. His white count was 11,600; neutrophils 62 per cent. Six weeks prior to this he had suffered acute pyelonephritis which had responded to sulfonamide therapy. The patient did well and was discharged, only to be readmitted 1 week later with the complaint of bilateral swelling and tenderness of the epididymis. On this admission the patient was afebrile; his white cell count was 10,600 with 60 polymorphonuclear cells. Excretory urogram and bilateral retrograde pyelogram were thought to be suggestive of renal tuberculosis on the basis of narrowing of an infundibulum in the left kidney. He was discharged receiving antituberculous triple drug therapy. Results of urine smears, cultures, and 2 guinea pig inoculation studies prior to therapy were negative for acid-fast bacilli.

On readmission the patient's chief complaint was fatigue. Tenderness and enlargement of the left epididymis and testicle were again present. His white count was 11,700 with 65 per cent polymorphonuclear cells. His urine contained no cells; serologic reaction for syphilis was negative, and again multiple cultures, smears, and guinea pig inoculation studies were negative for tubercle bacilli. Repeat excretory urogram and retrograde pyelogram revealed no change.

In view of laboratory failure to confirm the previous clinical diagnosis of renal and epididymal tuberculosis, it was elected to explore the left epididymis for diagnostic purposes. The head of the epididymis was found to be blue-grey, enlarged, and indurated. An epididymectomy was performed and pathologic examination revealed a spermatic granuloma (Fig. 2). Subsequently, the patient was discharged and is asymptomatic 1 year later.

A spermatic granuloma was incorrectly diagnosed as tuberculous epididymitis. The patient was spared antituberculosis treatment by establishment of the diagnosis by surgical exploration.

PATIENT 3. A 40 year old machinist was admitted to the hospital because of painful swelling of the right scrotal contents of 1 month's duration. In 1952, a right nephrectomy had been performed for renal tuberculosis. In 1953, a left epididymo-orchiectomy allowed demonstration of tuberculous infection by gross and histologic examination. His urine was found to be positive by guinea pig inoculation. He subse-

quently completed a year of streptomycin and para-aminosalicylic acid therapy.

On physical examination, the globus major of the right epididymis was found to be enlarged, indurated, and tender. Findings were otherwise not remarkable.

White blood cell count was 12,400 with 65 per cent polymorphonuclear cells. The urine contained a rare red cell in the sediment and was otherwise negative. Escherichia coli was cultured from a clean voided specimen. A roentgenogram of the patient's chest was negative.

In view of the persistent discomfort in the right epididymis, and the conversion of urinary acid-fast bacillus smear and culture to negative, exploration of the left epididymis was carried out. An epididymectomy was performed and pathologic examination revealed the 1 centimeter firm nodule in the body of the epididymis to be a spermatic granuloma (Fig. 3).

Despite a past history of proved genitourinary tuberculosis and clinical findings compatible with tuberculous epididymitis, this patient's lesion was demonstrated by exploration to be a spermatic granuloma without evidence of tuberculous infection.

TREATMENT

Conservative treatment with scrotal elevation and ice pack deserves an initial trial. Occasionally, persistent disabling pain due to spermatic granuloma may warrant epididymectomy for symptomatic relief. Surgical exploration carries little morbidity and is advisable when the diagnosis is uncertain and rests between tuberculous epididymitis, neoplasm, and spermatic granuloma. In view of the high incidence of this lesion in routine autopsy studies and the infrequency of correct clinical diagnoses, it is reasonable to believe that patients with spermatic granuloma are presently being treated for either tuberculous or suppurative epididymitis. Because a tissue diagnosis was obtained, Patients 2 and 3 were spared an unwarranted long term course of antituberculosis therapy. The importance of retrograde vasography and surgical exploration is evident.

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USE OF DIETHYLPROPION COMBINED WITH A SUPPLEMENT FOR SAFE AND EFFECTIVE WEIGHT CONTROL IN PREGNANCY

MICHAEL J. JORDAN, M.D., F.A.C.S., and GENEVIEVE M. BADER, M.D.,
New York, New York

THE AVERAGE WEIGHT GAIN during normal pregnancy is about 22 pounds. This increase is accounted for mostly by the gestational products, the hyperplasia and hypertrophy of associated reproductive organs, and by water and protein storage.

According to a statistical study by Brantley of 368 pregnancies, there was an average increase of 22.5 pounds for the entire period of gestation but 38 per cent of the women gained 25 pounds or more. In some of those who gained excessively, labor was prolonged over 24 hours or delivery was difficult.

During the latter 6 months of gestation the weight gain must be watched. The obese woman is predisposed to toxemia in the prenatal period, to dystocia, to increased difficulty in delivery, and frequently, to residual hypertension in the puerperium and beyond.

In a study by Thomson and Billewicz of 4,214 primiparas the occurrence of preeclamptic toxemia was 10 times as common in the group of women who gained more than 1.75 pounds per week between the twentieth and thirty-sixth weeks of pregnancy.

It is customary for physicians to set a limit of 18 to 20 pounds of weight gain for the entire period of pregnancy. Our personal experience indicates that the ideal weight gain during pregnancy is 12 to 15 pounds at the most, never over 20 pounds. This restriction not only improves the patient's comfort and appearance but also tends to prevent the complications often associated with obesity during gestation.

The greatest weight gains occur during the third trimester. This is also the time when the development of obesity may predispose to the complications of pregnancy and labor. The body weight increases in the last 3 months an average of 12.4 pounds; namely, 5.3 pounds in the seventh month, 3.7 pounds in the eighth month, and 3.4 pounds in the ninth month.

It is particularly important to control weight during the first pregnancy and thus establish a precedent for the patient's future guidance. After labor some of the excess weight is usually retained. With each successive gestation more pounds are added, some of which are never lost. These progressive gains finally lead to the problem of obesity.

METHODS OF WEIGHT CONTROL

Attempts to lose or control weight by dieting alone are notoriously unsuccessful. In a series, reported by Stunkard and McLaren-Hume, of 100 obese patients who were put on a 800 to 1,500 calorie diet at a New York nutrition clinic, only 12 succeeded in losing more than 20 pounds at any time during a 2 year period and 54 per cent complained of nervousness, weakness, irritability, fatigue, or nausea. This situation has led to the general use of appetite depressants for weight control.

The most widely used appetite depressant is d-amphetamine. It has serious disad-

From the Department of Obstetrics and Gynecology, St. Clare's Hospital, New York.

TABLE I.—WEIGHT CHANGES OF 50 GRAVID WOMEN TREATED WITH A COMBINATION OF ANOREXIGENIC AGENT AND NUTRITIONAL SUPPLEMENT

Case No.	*Age, yrs.*	*Gravida*	*Para*	*Weight change (previous pregnancy)*	*Weight change (prior to medication)*	*No. weeks on medication*	*Weight change (on medication)*	*Weight change per week (on medication)*	*Side effects*
1	37	4	3	+ 9	+ 7	10	+ 3.5	+0.35	0
2	42	1	0	—	+11.5	12	+ 6.5	+0.54	0
3	42	4	4	+10	+10	7	+ 1.5	+0.21	0
4	25	2	2	+30	+13	8	+ 1.5	+0.19	0
5	35	3	2	+19	+13	12	+ 9	+0.75	0
6	27	3	3	+14.5	+ 8	5	− 5	−1.00	0
7	18	2	0	—	+ 9.5	11	+ 5.5	+0.50	0
8	40	2	1	—	+ 6	13	+ 6	+0.46	0
9	32	1	0	—	+ 3	12	+ 4	+0.33	0
10	36	3	2	—	—	9	− 4	−0.44	0
11	32	3	2	+17	—	11	+ 3.5	+0.32	0
12	29	4	2	+22	—	15	+ 2	+0.13	0
13	25	2	2	—	+ 5.5	13	+ 5	+0.38	0
14	37	2	1	+17	—	8	− 6	−0.75	0
15	28	3	2	+20	+21	9	−10.5	−1.17	0
16	31	3	1	+28	—	16	+ 5	+0.31	0
17	30	1	0	—	+ 5	13	+ 5	+0.38	0
18	27	2	0	—	—	12	+ 2.5	+0.21	0
19	29	1	0	—	—	10	+ 6.5	+0.65	0
20	17	1	1	—	+16	7	+ 5	+0.71	0
21	27	1	0	—	+ 5	12	− 4	−0.33	0
22	35	2	1	—	+ 7	16	+ 6	+0.38	0
23	36	1	0	—	+16	8	− 6	−0.75	0
24	24	2	1	+26	+14	6	−10	−1.67	0
25	41	3	2	+24	+ 8	10	+ 4	+0.40	0
26	19	1	0	—	+ 4	11	+ 5	+0.45	0
27	25	2	2	+28	+14	9	−10	−1.11	0
28	27	3	2	+20	+12	6	− 6	−1.00	0
29	38	1	0	—	+16	8	− 8	−1.00	0
30	21	2	1	+34	+17	10	− 9	−0.90	0
31	32	1	0	—	+ 6	6	0	0.00	0
32	42	3	2	+28	+14	7	− 4	−0.57	0
33	35	1	0	—	+ 4	4	+ 2	+0.50	0
34	20	2	1	+22	+18	8	−10	−1.25	0
35	37	4	3	+26	+20	6	−10	−1.67	0
36	29	2	1	+24	+12	6	− 5	−0.83	0
37	23	1	0	—	+ 9	4	− 2	−0.50	0
38	36	3	2	+26	+14	7	− 6	−0.86	0
39	31	2	1	+19	+10	5	− 4	−0.80	0
40	22	2	0	+30	+14	7	− 7	−1.00	0
41	34	3	4*	+38	+12	10	− 2	−0.20	0
42	26	1	0	—	+ 6	4	+ 1	+0.25	0
43	38	4	3	+24	+ 8	10	− 6	−0.60	0
44	33	3	2	+17	+ 7	6	− 4	−0.67	0
45	29	2	1	+12	+ 8	5	+ 2	+0.40	0
46	34	6	5	+24	+12	6	0	0.00	0
47	36	2	1	+26	+14	5	− 3	−0.60	0
48	24	3	1	+26	+12	6	− 3	−0.50	0
49	40	2	1	+24	+ 6	4	− 2	−0.50	0
50	19	1	0	—	+ 4	3	− 1	−0.33	0
Aver.	30.6	2.3	1.3	+22.8	+10.5	8.6	− 1.1	−0.24	0

*Twins

vantages because of its sympathomimetic action and stimulation of the central nervous system. Nervousness, confusion, and insomnia are common side reactions.

The contraindications to d-amphetamine include hyperexcitability, agitated prepsychotic states, coronary or cardiovascular disease, and severe hypertension.

DIETHYLPROPION

Diethylpropion is the generic name of a new appetite depressant which has been studied pharmacologically and clinically in Germany and Ireland with confirmation of these results in the United States.

The anorexigenic effect of diethylpropion, with resulting weight control, compares favorably with that of d-amphetamine. Diethylpropion, however, has the following important advantages: (1) There is slight stimulation of the central nervous system. Hence the symptoms of restlessness, nervousness, and inability to relax, so commonly observed with d-amphetamine, are notably absent with use of diethylpropion. (2) There is no cardiac toxicity and the effect on blood pressure is insignificant. (3) The duration of the anorexigenic effect of diethylpropion is more than 4 hours as compared with less than 3 hours for amphetamine.

In a clinical evaluation of diethylpropion reported by Spielman in a group of 70 patients without any diet instructions, 88 per cent had a satisfactory suppression of appetite and lost an average of 1.29 pounds weekly. The incidence of side effects was extremely low and the drug could be administered in the evening without interference with sleep.

It has been shown by Huels that diethylpropion is helpful in decreasing the often torturing hunger of the patient whose food intake is strictly reduced and that the drug can be added to the therapy of obesity even in the presence of cardiovascular and other complicating organic diseases.

In an evaluation of anorexigenic products by Ravetz, diethylpropion was found to be a safe, well tolerated, clinically effective drug for the suppression of appetite in all age groups of patients. Twenty-eight of a group of 32 patients (87.5 per cent) demonstrated a satisfactory weight reduction pattern, and adverse side reactions were encountered in only 3 cases, mild gastrointestinal disturbance in 2, and central nervous system stimulation in 1.

Because of its demonstrated safety and the virtual absence of side effects, diethylpropion in doses of 25 milligrams was combined with a well established nutritional supplement and used especially as a means of controlling weight gain during pregnancy.

The dosage schedule provides for 1 tablet 3 times daily 1 hour before meals, with a fourth tablet at mid-evening if required to control appetite.

As reported by Nulsen, this combination was administered to 138 pregnant women of whom 105 continued treatment long enough for therapeutic evaluation. The results were as follows: actual loss of weight in 7 cases (6.7 per cent), no weight gain in 11 cases (10.5 per cent), gain of less than 3 pounds per month in 55 cases (52.4 per cent), gain of more than 3 pounds per month in 32 cases (30.5 per cent). In a comparison of various methods of weight control during pregnancy, the average weight gain for the entire period of gestation was 17.2 pounds with the medication as compared with figures ranging from 20.5 to 29.0 pounds for the other methods. As previously stated, the recommended limit is 12 to 15 pounds.

There were no deleterious effects upon any of the babies and side effects were uncommon: nausea in 4 cases, nervousness in 4, increased hunger of short duration, occurring about 15 minutes after medication in 4, insomnia in 1 (only after night dose), weakness or fatigue in 1, and headache in 1. Even when given in 4 times the recommended dosage, diethylpropion produced no deleterious effects upon blood pressure, heart rate, or the electrocardiogram.

PRESENT STUDY

The study group included 50 gravid women ranging in age from 17 to 42, average 30.6 years. As to the history of previous pregnancies, 14 were gravida 1, 17 gravida 2, 13 gravida 3, 5 gravida 4, and 1 gravida 6, average 2.3. As to childbirths, 16 were para 0, 14 para 1, 13 para 2, 4 para 3, 2 para 4, and 1 para 5, average 1.3.

The usual dosage was 1 tablet 1 hour before meals, with an additional tablet in the mid-evening if needed to control appetite. None of the patients knew that an appetite depressant was being used. They thought that the tablets were merely a vitamin supplement. No specific diet was prescribed. The patients were told to limit salt, starches, and fluids.

RESULTS

The details of the results are shown in Table I.

The range of weight gains in previous pregnancies was 9 to 38 pounds, average 22.8 pounds. Prior to starting treatment with medication the weight gains ranged from 3 to 21 pounds, average 10.5 pounds.

The period of treatment ranged from 3 to 16 weeks, average 8.6 weeks. On this regimen 22 patients had total weight gains ranging from 1 to 9 pounds, while 26 had total weight losses ranging from 1 to 10.5 pounds. In 2 cases there was no weight change. The average total weight loss was 1.1 pounds.

The average weekly weight loss for the entire group under treatment was 0.24 pound. This figure was obtained by averaging the results obtained in each of the individual cases.

There were no side reactions or allergic manifestations in any case. Insomnia did not occur, even in 2 cases in which the patients took the medication in the evening. All patients mentioned a sense of well-being. There were no significant changes in blood pressure or pulse rate during the period of medication. No change in rate or rhythm of fetal heart was noted.

All deliveries were normal with healthy babies with the exception of Case 5, which was complicated by an Rh factor.

SUMMARY

A combination of the new appetite depressant, diethylpropion, with supplemental vitamins and minerals was evaluated clinically in a group of 50 gravid women and confirmed previous reports of its value for safe and effective weight control in pregnancy. The recommended dosage schedule is 1 tablet 3 times daily 1 hour before meals, with a fourth tablet at mid-evening if required to control appetite. No special diet was prescribed in any case. When this medication was used for an average period of 8.6 weeks, there was an average weight loss of 0.24 pound per week.

There were no side reactions or allergic manifestations in any case. Diethylpropion does not produce central nervous system stimulation, insomnia, or any significant change in the blood pressure or pulse rate.

All deliveries were normal with healthy babies with the exception of Case 5 which was complicated by an Rh factor.

The convenience of using an appetite depressant in combination with a vitamin-mineral supplement in a single tablet has obvious advantages.

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ASCORBIC ACID IN THE BIOSYNTHESIS AND MAINTENANCE OF COLLAGEN

RONALD W. CHEN, Ph.D., and R. W. POSTLETHWAIT, M.D., F.A.C.S.,
Durham, North Carolina

ASCORBIC ACID is necessary for the biosynthesis of collagen, but the evidence for its role in the maintenance or turnover of collagen has been equivocal. Based upon histologic findings, Hunt and Pirani and Levenson indicated a possible reversion of collagen to "precollagen" in guinea pig wound tissue if normal animals were deprived of vitamin C. Elster and Robertson (20), however, reported that preformed collagen was stable. The methods used, however, did not assure the measurement of only collagen.

Collagen is unique among proteins of mammalian tissues in that it contains hydroxyproline. This study was focused upon the quantitation of the relationship between proline and hydroxyproline in newly grown connective tissue as a function of the dietary level of ascorbic acid. Connective tissue growth was induced by the subcutaneous implantation of polyvinyl sponges into guinea pigs. The data presented show a requirement for ascorbic acid in the development and maintenance of normal hydroxyproline levels in sponge implant tissue.

METHODS

Male guinea pigs weighing 250 to 300 grams were used in these experiments. The number of animals in each experimental group is indicated in the illustrations and tables.

Normal diet consisted of rabbit pellets (purina) and cabbage. Groups of animals were made scorbutic by maintaining them on a Sherman scurvy diet which was supplemented by multivitamin mixtures without ascorbic acid.

The polyvinyl sponge (ivalon) was freed from the formaldehyde preservative, dried, weighed, and autoclaved before implantation. In general, 4 sponges measuring 2 centimeters square and 0.3 centimeter thick were implanted subcutaneously in each guinea pig under aseptic conditions. Each sponge was used for a separate determination to be described later. Scorbutic animals were operated on 14 days after the scurvy diet was started since at this time their tissues were essentially depleted of ascorbic acid.

When scorbutic animals were treated with vitamin C, 1 milliliter of a solution containing 20 milligrams of ascorbic acid was administered intraperitoneally each day. The amount of food available to these guinea pigs was limited to their previous average daily intake before ascorbate treatment was begun.

Normal guinea pigs were sacrificed 2, 4, 7, 14, 21, 28, 35, 42, and 56 days postoperatively. The diets of 4 groups of normal animals were changed to the scorbutigenic food 21 days after operation. Autopsies were performed on these animals 1, 2, 3, or 4 weeks later, i.e., 28, 35, 42, or 49 days after implantation.

The scorbutic animals were sacrificed 2, 4, 7, 14, and 21 days after sponge implantation. Studies could not be extended beyond 21 days as practically no animals survive longer than this, i.e., 5 weeks on the Sherman diet. Other groups of scorbutic

From the Department of Surgery, the Veterans Administration Hospital and the Duke Medical Center, Durham.
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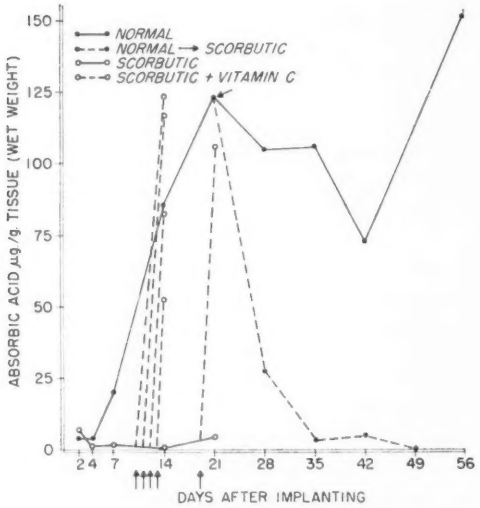

FIG. 1. Ascorbic acid content of ingrown connective tissue obtained from normal and scorbutic guinea pigs. Four groups of normal animals were placed on a scorbutogenic diet on the twenty-first postoperative day, upper arrow. The lower arrows indicate when groups of scorbutic animals were treated with 20 milligrams of ascorbic acid per day for 1 to 4 days. Each point represents the mean value obtained from 5 to 16 animals.

guinea pigs were given ascorbic acid for 1 to 4 days beginning 7, 10, 11, 12, 13, or 19 days after operation, as indicated in Figure 1.

The animals were sacrificed by the administration of nembutal. One sponge from each animal was immediately weighed, cut into small pieces, and ground with sand and 4 per cent trichloroacetic acid. The ascorbate content of the ingrown tissue was then determined by the dinitrophenylhydrazine method of Roe, Mills, Oesterling, and Damron.

For a period of 8 hours 2 of the sponges were placed into separate jars which contained acetone. The acetone was changed and, after an additional 16 hours, decanted off. The sponges were then placed in ether for 24 hours. After the ether was removed, the sponges were dried for 2 hours at 110 degrees and weighed to determine the amount of dry tissue present. Both dry and wet weights of tissue were assumed to be the weight increment of the implanted sponges. Sponges not implanted into guinea pigs were treated with organic solvents as just described. In none of the sponges was there weight loss due to this procedure. One of these implants was hydrolyzed with hydrochloric acid and total hexosamines determined as described by Boas. Collagen was extracted as gelatin from the other implant by two extractions in an autoclave for 3 hours at 15 pounds pressure. The extracts and washes were evaporated to dryness. Residues were hydrolyzed with 6 normal hydrochloric acid for 3 hours at 135 degrees in sealed tubes, and the hydroxyproline content was determined as described by Neuman and Logan and the proline content by the method of Troll and Lindsley. Proline and hydroxyproline analyses were also done on hydrolysates of the nonextractable or residual portion.

The remaining sponge was fixed in neutral formalin in preparation for histologic studies.

RESULTS

The ascorbic acid present in the newly forming connective tissue is presented in Figure 1. In the normal animal, low levels of this vitamin were found up to at least the fourth day. Coincident with this were the low levels of extractable hydroxyproline (Fig. 2). At this time, the sponges were only sparsely invaded by erythrocytes, leukocytes, and fibroblasts. By the seventh day, a significant increase in vitamin C was noted. This increase continued until about the twenty-first day, after which the ascorbic acid content leveled off. Hydroxyproline did not increase significantly until after the seventh day. Between the seventh and fourteenth days, the hydroxyproline level began to increase sharply and continued to rise throughout the experimental period. Hydroxyproline paralleled the ascorbate rise between the seventh and twenty-first days.

In the scorbutic guinea pigs, negligible amounts of vitamin C were found throughout the experimental period (Fig. 1). Little or no collagen was formed without this

vitamin (Fig. 2). Ascorbic acid administered to scorbutic animals was taken up by the connective tissue and collagen synthesis ensued, as indicated by the fact that 1 dose of 20 milligrams of ascorbate was sufficient to bring about a significant increase in the extractable hydroxyproline content in 24 hours. Apparently, no diminution occurred in the ability of the connective tissues of scorbutic animals to recover the collagen synthesizing capacity when treated with ascorbic acid as late as the nineteenth postoperative day.

When the Sherman diet was given to normal animals, a precipitous drop in the vitamin C content of the ingrown tissue followed, reaching minimal levels by the fourth week (Fig. 1). Collagen formation, however, continued at control rates the first week after the animals were placed on the scorbutogenic diet (Fig. 2). Between the first and second week the hydroxyproline concentration remained unchanged and by the third week had been partially depleted. The hydroxyproline level continued to decrease at the fourth week.

In the normal animal, the level of nonextractable hydroxyproline, which may represent the elastin content of the tissue, was approximately 1 micromol per gram dry weight of tissue during the end of the first week (Table I). This slowly increased to about 6 micromoles per gram by the fifty-sixth day. In scorbutic guinea pigs, the residual hydroxyproline varied from 1 to 3 micromols, which represents 12 to 59 per cent of the total hydroxyproline present in the scorbutic tissue. In normal tissue, the residual hydroxyproline ranged from 0.8 to 10.6 per cent.

The extractable proline concentration increased about twofold from the second to the fourth days in both normal and scorbutic tissue (Fig. 3), possibly due to infiltrating plasma proteins rather than proteins produced by fibroblasts. This increase was followed by a significant decrease by the seventh day, more so in the scorbutic tissue than in the normal. In the normal,

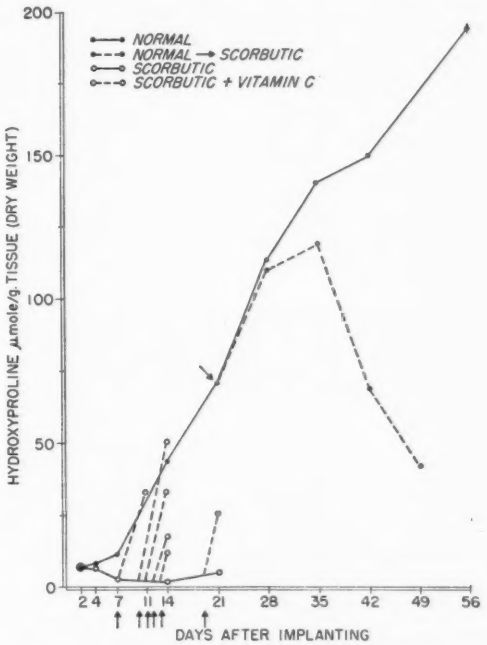

FIG. 2. Hydroxyproline content of hydrolysates of autoclaved aqueous extracts of ingrown connective tissue. Four groups of normal guinea pigs were placed on a scorbutogenic diet on the twenty-first postoperative day, upper arrow. The lower arrows indicate when groups of scorbutic animals were treated with 20 milligrams of ascorbic acid per day for 1 to 4 days before sacrifice. Each point represents the mean value obtained from 5 to 16 guinea pigs.

from the seventh to the twenty-first days the proline level remained fairly constant and then increased steadily to the eighth week. In the scorbutic, proline content remains essentially unchanged between the first and second week and then apparently increases. Treating scorbutic guinea pigs with ascorbic acid tended to increase the extractable proline and, conversely, placing normal animals on a vitamin C deficient diet tended to decrease this fraction by the third week after the diet change. Whereas the extractable hydroxyproline is due to collagen alone, the extractable proline is contributed to by other proteins as well as collagen. This is evidenced by the molar proline:hydroxyproline ratio. Isolated collagen has been reported by Eastoe and

TABLE I.—RESIDUAL HYDROXYPROLINE

Days	*Normal, micromols/gm.*	*Scurvy, micromols/gm.*	*Days*	*Normal animals on scurvy diet, micromols/gm.*	*Scorbutic animals treated with ascorbic acid, micromols/gm.*
2	0.83 ± 0.22	1.12 ± 0.18	21+S7	6.22 ± 1.71	
4	0.06 ± 0.12	0.85 ± 0.38	21+S14	6.70 ± 0.94	
7	1.28 ± 0.25	1.52 ± 0.10	21+S21	6.12 ± 1.12	
14	3.33 ± 0.92	1.88 ± 0.06	21+S28	13.9 ± 9.52	
21	4.26 ± 1.22	2.95 ± 0.95			
28	8.60 ± 4.41		7+N4		2.12 ± 0.62
35	5.30 ± 1.04		10+N4		3.04 ± 0.61
42	7.10 ± 4.42		11+N3		3.42 ± 1.15
56	6.40 ± 1.56		12+N2		2.40 ± 0.51
			13+N1		3.08 ± 0.44
			19+N2		2.45 ± 1.36

Hydroxyproline determinations were made on material which could not be extracted by autoclaving connective tissue in the presence of water. Each value is the mean ± standard deviation obtained from 5 to 16 guinea pigs. "Days" refers to the number of days after polyvinyl sponges were implanted. Under "Scorbutic treated with ascorbic acid", 7 + N4 means that the animals began receiving ascorbic acid on the 7th postoperative day and were treated for 4 days. Under "Normal animals on scurvy diet", 21+S7 means that the animals were put on a scorbutogenic regimen on the twenty-first postoperative day and were sacrificed 7 days later. Scorbutic animals that were given ascorbic acid received 20 milligrams a day. Results are expressed in micromols per gram of tissue, dry weight.

TABLE II.—TISSUE GROWTH

Days	*Normal, mgm. tissue/ mgm. sponge*	*Scurvy, mgm. tissue/ mgm. sponge*	*Days*	*Normal animals on scurvy diet, mgm. tissue/ mgm. sponge*	*Scorbutic animals treated with ascorbic acid, mgm. tissue/ mgm. sponge*
2	0.31 ± .06	0.30 ± .10	21+S7	0.71 ± .33	
4	0.33 ± .08	0.39 ± .10	21+S14	0.48 ± .12	
7	0.47 ± .14	1.03 ± .34	21+S21	0.61 ± .24	
14	0.82 ± .20	1.30 ± .31	21+S28	0.28 ± .16	
21	0.80 ± .20	0.83 ± .20			
28	0.76 ± .34		7+N4		0.82 ± .16
35	0.76 ± .23		10+N4		0.94 ± .20
42	0.76 ± .30		11+N3		0.99 ± .23
56	0.55 ± .21		12+N2		1.06 ± .27
			13+N1		1.16 ± .29
			19+N2		0.68 ± .28

The amount of tissue—milligrams dry weight—per milligram of sponge implanted was used as a crude measure of growth. The values are the means ±standard deviation obtained from 10 to 92 sponges. "Days" refers to the number of days after polyvinyl sponges were implanted. Under "Scorbutic treated with ascorbic acid", 7+N4 means that the scorbutic animals began receiving ascorbic acid on the seventh postoperative day and were treated for 4 days. Under "Normal animals on scurvy diet", 21+S7 means that the normal animals were put on a scorbutogenic regimen on the twenty-first postoperative day and were sacrificed 7 days later. Scorbutic animals that were given ascorbic acid received 20 milligrams a day.

Leach, and by Jackson, Leach, and Jacobs, to have a proline:hydroxyproline ratio of about 1 to 1.5. In normal connective tissue obtained from implants, the ratio was initially about 30 (Fig. 4), and this ratio reduced to approximately 2 by the eighth week. In scorbutic tissue, the ratio of the extractable material remained high at about 30 to 45 throughout the experimental period.

With the exception of one point, scorbutic animals given ascorbic acid at the nineteenth postoperative day, administration of vitamin C to scorbutic animals tended to decrease nonextractable proline levels, whereas development of scurvy in normal animals tended to increase this fraction (Fig. 5).

The total proline content, extractable plus residual proline, of the tissues of scorbutic guinea pigs was not significantly different from the content of the normal tissue.

DISCUSSION

The need for ascorbic acid in the biosynthesis of collagen has been well established. Recent reviews are those of Jackson (12), and Edwards and Dunphy (4, 5). The evidence reported herein confirms this concept. The vitamin C content of the ingrown connective tissue parallels, if not actually precedes, the formation of collagen. In our previous communications (19, 24) it was shown that ascorbic acid accumulates in wound tissue to a greater extent than in adjacent uninjured tissue. Injection of ascorbic acid directly into the implanted

sponge has been shown by Gould (7) to enhance collagen synthesis. These results suggest that this vitamin may function directly in the connective tissue.

The results presented herein bear especially upon the question of whether or not ascorbic acid is required to maintain collagen once it is formed and also upon the nature of the collagen precursor. Using histologic techniques, Hunt and later Pirani and Levenson indicated that reversion of collagen to "precollagen" occurred in healing wounds of normal guinea pigs if these animals were given a scorbutogenic diet. Contradictory results were obtained by Elster and by Robertson (20) with respect to the maintenance of collagen content in guinea pig organs. These investigators found that preformed collagen of normal animals, as isolated by the method of Lowry, Gilligan, and Katersky, was not decreased in various guinea pig organs when the animals were placed on the vitamin C deficient diet. Robertson (22) reaffirmed his conclusions with respect to carrageenin induced connective tissue. These findings rest on the assumption that only collagen is present when using this method of isolation. The colorimetric method for determining hydroxyproline as described by Neuman and Logan afforded a more direct measure of the changes in collagen concentration. Three weeks postoperatively, 4 groups of normal guinea pigs were deprived of ascorbic acid. One week later, collagen synthesis, as determined by the hydroxyproline present, continued at normal rates (Fig. 2). At this time the ascorbic acid content of the tissue had been markedly reduced but still contained an amount that had supported rapid collagen synthesis in the early stages after sponge implantation (Fig. 1). The essentially complete depletion of vitamin C by the second week on a scurvy-producing diet corresponded either to a cessation of collagen formation or to a balance between its synthesis and destruction. By the third week, definite evidence of collagen dissolution appears. Recently, Gould (8) has reported similar observations. It would seem, then, that vitamin C is required for the maintenance of the established collagen level. The failure of collagen biosynthesis in the face of normal rates of dissolution could account for a drop in the net collagen level upon ascorbic acid withdrawal. This interpretation would require a relatively high turnover rate for the collagen formed in these experiments.

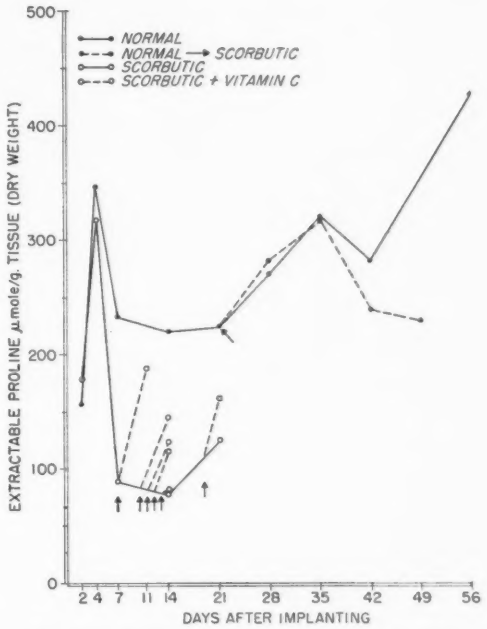

FIG. 3. Proline content of hydrolysates of autoclaved aqueous extracts of ingrown connective tissue. Four groups of normal guinea pigs were started on a scorbutogenic diet on the twenty-first postoperative day, upper arrow. The lower arrows indicate when groups of scorbutic animals were treated with 20 milligrams of ascorbic acid per day for 1 to 4 days before sacrifice. Each point represents the mean value obtained from 5 to 16 guinea pigs.

A variety of "precursors" of collagen have been reported by Orekhovich and associates (16, 17), Highberger and associates, and Gould and Woessner (9). No doubt there are several stages in this biosynthetic pathway, each involving a "precursor." Part of the current investigation and subsequent work to be reported are concerned

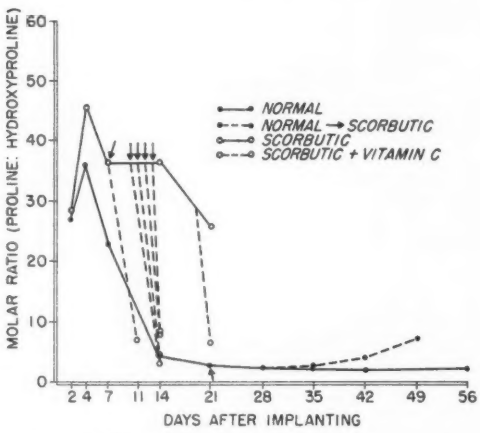

FIG. 4. Molar ratio, proline:hydroxyproline, in hydrolysates of autoclaved aqueous extracts of ingrown connective tissue. Four groups of normal guinea pigs were placed on a scorbutogenic diet on the twenty-first postoperative day, lower arrow. The upper arrows indicate when groups of scorbutic animals were treated with 20 milligrams of ascorbic acid per day for 1 to 4 days before sacrifice. Each point represents the mean value obtained from 5 to 16 guinea pigs.

with the conversion of proline to hydroxyproline. Since Stetten and Schoenheimer (26, 27) showed that fed proline but not hydroxyproline was extensively incorporated into carcass protein, one assumption has been that proline may be peptide-bound before its hydroxylation is brought about. Gould and Woessner (9) obtained evidence of a high proline containing fraction since the extraction of collagen by autoclaving resulted in more proline than could be accounted for by collagen. This "excess proline" in scorbutic animals treated with ascorbic acid is reduced as hydroxyproline is formed. However, amino acid analyses of autoclaved aqueous extract and tannic acid-precipitable proteins of scorbutic carrageenin granuloma revealed an amino acid pattern inconsistent with that of a likely precursor. The amino acid compositions differed from that of collagen and did not contain exceptionally large amounts of either proline or glycine. Based upon their radioisotope studies, Robertson, Hiwett, and Herman (21), suggest that bound hydroxyproline is not derived from proline which is part of a large molecule.

From the molar ratio, proline:hydroxyproline (Fig. 4) of the extractable material, it is evident that the proline can be attributed to other sources in addition to collagen. With time, collagen becomes the major source of this amino acid in normal connective tissue. On the other hand, in scorbutic tissue there is an abundance of extractable proline but little or no collagen (Fig. 2). The fact that within 1 day after scorbutic animals are treated with ascorbic acid the proline:hydroxyproline ratio changes from in excess of 30 to about 7.5 indicates that collagen precursors are readily available to the tissue. In a similar experiment, Gould and Woessner (9) found that a 60 microgram hydroxyproline production was accompanied by a 50 microgram loss in total extractable proline and a loss of 115 micrograms of proline not attributable to collagen. This observation strongly supports the high proline containing precursor hypothesis. If the data presented in the present investigation are calculated in a similar manner, such stoichiometric relationships are not obtained. It would seem such a relationship could ideally be realized only if: (a) the connective tissue at the time of observation were an isolated system, not subject to incoming proteins nor to an exchange of proteins, (b) there be no *de novo* synthesis of proteins such as the collagen precursors, (c) the nonextractable proteins not be a source of the extractable proteins, and (d) no change develop in the cellular population or pattern. To examine this problem further, we are fractionating the extractable proteins under varying conditions, and preliminary data indicate the presence at any particular time of a series of separable extractable proteins with varying proline:hydroxyproline ratios. The purity and nature of these fractions are not yet ascertained, but the data suggest the presence of a high proline containing precursor of collagen.

The inability of scorbutic tissue to syn-

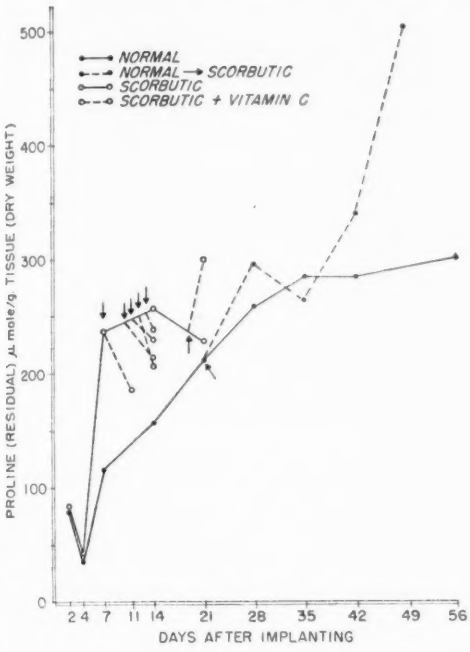

FIG. 5.

FIG. 5. Proline content of hydrolyzed, nonextractable material of ingrown connective tissue. Four groups of normal guinea pigs were placed on a scorbutogenic diet on the twenty-first postoperative day, arrow on extreme right. The other arrows indicate when groups of scorbutic animals were treated with 20 milligrams of ascorbic acid per day for 1 to 4 days before sacrifice. Each point represents the mean value obtained from 5 to 16 guinea pigs.

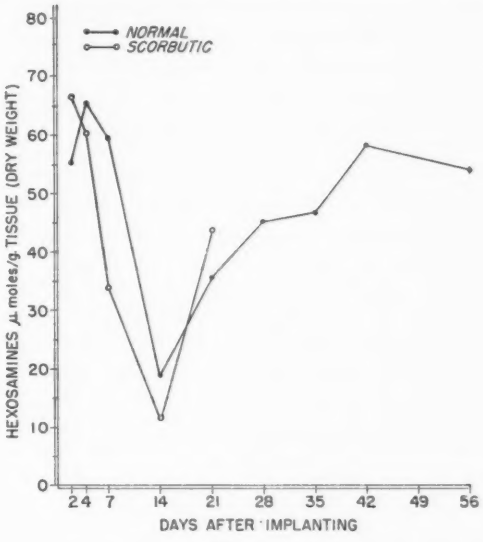

FIG. 6.

FIG. 6. Hexosamine content of ingrown connective tissue obtained from sponges implanted into normal and scurvy guinea pigs. Each point represents the mean value obtained from 6 to 36 guinea pigs.

thesize collagen is not due to an absence of fibroblasts. Histologic sections showed an abundance of fibroblasts. A crude measurement of growth into the sponge was attempted by tabulating the amount of dry weight of tissue per milligram of implanted sponge (Table II). Apparently growth had reached a peak between the first and second week and then leveled off in the normal guinea pig. Scorbutic "growth" was more extensive than normal between the first and second week and then actually regressed.

In studying wound healing in normal rats, Dunphy and Udupa found an inverse relationship in the collagen and total hexosamine concentrations. Initially high hexosamine content corresponded to a lag phase in collagen synthesis. As the hexosamine concentrations decreased, collagen synthesis increased. Their studies covered a 15 day healing period. The results of the experiments reported herein are similar for a comparable period of observation (Figs. 6 and 2). After the second week, however, there was a steady rise in hexosamine content until about the sixth week in the normal tissue. Tissue from scorbutic animals followed a similar pattern, but for the most part at a somewhat lower level than normal. The total hexosamine in the tissue does not allow a unique interpretation of the polysaccharide changes. Identification of the actual types and amount of polysaccharide present under different conditions would probably yield more useful information.

SUMMARY

Connective tissue obtained by the sponge implant method was used to study the role of ascorbic acid in the biosynthesis of col-

lagen as determined by hydroxyproline analysis. Extractable hydroxyproline paralleled the ascorbic acid present in the connective tissue. Deprivation of this vitamin in guinea pigs which had already synthesized new collagen resulted in the depletion of this amino acid. The findings are consistent with the concept that this vitamin is necessary for the maintenance of established levels of at least newly formed collagen.

An inverse relationship between hexosamine and collagen content in normal guinea pigs was found only in the early stages of tissue formation. The general pattern of hexosamine present in scorbutic tissue was not unlike that found in normal tissue.

The possibility of a high proline containing polypeptide being a collagen precursor is discussed.

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THE SELECTIVE REMOVAL OF TRANSFUSED, COMPATIBLE ERYTHROCYTES FROM THE CIRCULATION OF NORMAL DOGS

D. B. ROCHLIN, M.D., Los Angeles, California, HOWARD RAWNSLEY, M.D., JOHN H. DUHRING, M.D., and WILLIAM S. BLAKEMORE, M.D., F.A.C.S., Philadelphia, Pennsylvania

IN THE ABSENCE of antigenic incompatibility, the survival of transfused undamaged erythrocytes has been shown by Ebaugh and by Read and their associates to approximate the survival of the recipient's own erythrocytes. Damaged erythrocytes are removed from the circulation within a short period after transfusion, according to Talbot and coworkers, whereas viable cells are retained for the normal life span of that cell. The longevity of these transfused cells has been demonstrated using both the Ashby (6) and the radioactive chromium-tagged erythrocyte techniques. This same survival pattern has been found in mongrel dogs by Hamilton (5) and Melnick and associates.

Recently, we (11) have studied the survival of erythrocytes which were transfused intraperitoneally in dogs and have found that a normal erythrocyte survival time follows autologous or homologous intraperitoneal transfusion of small quantities of blood. During the course of these studies we noted a phenomenon of the selective removal of transfused red cells which appeared to occur in the absence of any detectable antigen-antibody reaction of either the hemagglutinin or hemolysin type. This reaction appeared to be similar to that reported by Jandl and Greenberg, Goudsmit and Krijnen, and Fudenberg and Allen, all of whom reported the phenomenon in man after transfusion of apparently compatible red cells. The transfused cells showed a normal survival curve for periods of 10 days to 2 weeks after transfusion, but after this period of time were selectively removed from the circulation. In these reports, both donor and recipient cells and plasma were compatible in both major and minor blood groups. Jandl and Greenberg also demonstrated that the cells were sequestrated in the spleen prior to their complete disappearance from the body. No evidence of circulating antibody could be demonstrated. Swisher and Young reported the occurrence of a similar reaction in dogs that had been repeatedly transfused with erythrocytes from the same donor animal. In that report, a gradually shortening survival time was noted upon the repeated transfusion of radioactive chromium-tagged erythrocytes. These investigators considered this reaction to be of the agglutination type from the nature of the survival curves in these experiments but could not demonstrate circulating antibodies. Swisher and Young, cited by Mollison, later reported a similar type of transfusion reaction which appeared to be of a hemolytic type but they were able to show a circulating antibody.

A similar reaction was noted to follow some instances of the intraperitoneal transfusion of large quantities of blood in dogs, and this report is related to further studies of the phenomenon of selective destruction of apparently compatible transfused cells.

METHODS

Healthy mongrel dogs weighing 25 to 35 pounds each, with a peripheral circulating hemoglobin concentration of 12 grams

From the Harrison Department of Surgical Research and the William Pepper Laboratory, University of Pennsylvania, School of Medicine, Philadelphia, and the Department of Surgery, University of California School of Medicine, Los Angeles.

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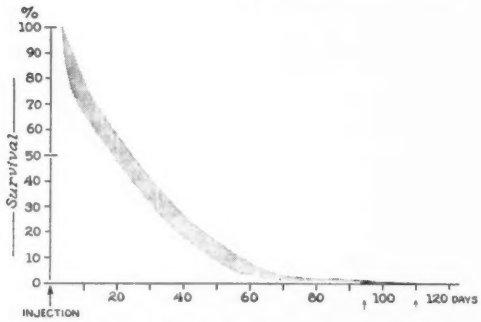

FIG. 1. Composite of 5 erythrocyte survival curves after intravenous injection of 50 milliliters of homologous radioactive chromium-tagged erythrocytes.

per cent or greater, were used in this study. Insofar as could be ascertained, none of these animals had ever been transfused or used as an experimental animal prior to this time. The donor dog and prospective recipients were selected at random for each experimental group. A sample of blood from each animal was typed for A positive or A negative antigenicity using the serum and methods of Young. Crossmatches of both major and minor types were made in saline and albumin in a 37 degree C. water bath. If these tests showed compatibility, a further test was made of direct Coombs type using rabbit produced anticanine serum.

The donor animal was then exsanguinated and an aliquot of the whole blood was frozen using a glycerol technique for subsequent serologic testing. The remainder of the cells were tagged with radioactive chromium according to Talbot's modification of the original Gray and Sterling technique. The prepared blood was then given to the recipients through a cannula placed in the greater saphenous vein, or it was used for the experiments employing intraperitoneal transfusions, according to the techniques previously described by us.

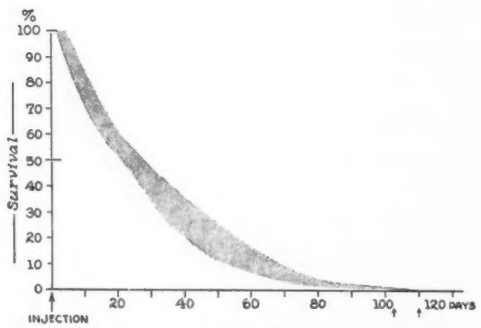

FIG. 2. Composite of 5 erythrocyte survival curves after intraperitoneal injection of 50 milliliters of homologous radioactive chromium-tagged erythrocytes.

Samples of peripheral blood were obtained at suitable intervals for the remainder of the experiment. The samples were analyzed for hemoglobin concentration using the cyanmethemoglobin method, in a spectrophotometer, and, for radioactivity, in a well type of scintillation counter. If, at any time during the course of the experiment, there was an abrupt lowering of the concentration of circulating donor cells, as shown by a change of decay-corrected radioactivity present, a crossmatch and a Coombs test were made using thawed reconstituted donor cells and fresh recipient plasma.

The effect of previous exposure of the recipient to donor red cell protein was investigated by injecting a group of 4 dogs with 2 deep intramuscular injections of 10 milliliters of washed hemolyzed donor cells 4 weeks and 3 weeks, respectively, prior to transfusion.

Another group of 4 dogs was subjected to splenectomy and then allowed to recover for a period of 2 to 3 months until the postoperative anemia was corrected with a return of hemoglobin concentrations to normal levels. The postoperative anemia was treated by intravenous injections of saccharated iron and folic acid. At the end of the recovery period, all of these splenectomized animals had hemoglobin concentrations which were again considered within the normal range.

A group of 6 animals was bled 500 milliliters, then transfused intraperitoneally with 500 milliliters of homologous tagged cells.

At the termination of each experiment, the animals were sacrificed, and aliquots of the spleen, liver, bone, lung, lymph nodes, and kidney were taken. These were homo-

genized and analyzed for concentration of radioactivity in a well scintillation counter. Histologic sections were examined after being stained with hematoxylin and eosin.

In analyzing the blood specimens taken, the count rate of the samples was corrected for the natural decay of radioactive chromium prior to graphically plotting the percentage of tagged cells that remained in the circulation after transfusion. In previous reports by other investigators, survival time has been determined by plotting a number of points representing the concentration of isotope in the samples of peripheral blood obtained at varied intervals after injection. From these figures a "zero-time value" was determined by extrapolation. A departure from this usual procedure has been made in this study and in our previous study concerned with intraperitoneal transfusion, since the maximal concentration of tagged cells, equivalent to the extrapolated zero-time value, in the animals injected intraperitoneally is not found in the peripheral circulation until 48 to 96 hours after injection. If this value were taken as the zero-time value and compared with the calculated value in the animals injected intravenously, it would show an apparently longer T ½[1] and a longer survival time for the cells injected intraperitoneally. This error would occur because the zero-time value for the intravenously injected cells includes those erythrocytes which have been traumatized, and these cells are removed from the circulation within a relatively short time after transfusion. If the maximum blood concentration found when the cells are injected intraperitoneally is considered the zero-time value, this does not include injured or dead cells, since these have already been removed from the circulation at the time of sampling. For this reason, and because the average time of maximum concentration of tagged cells in the blood stream of the animals injected intraperitoneally has been found to be about 72 hours, the concentration of the labeled erythrocytes found in the 72 hour sample drawn from dogs injected intravenously has been used as the zero-time value. It is believed that the small changes in the T ½ and the ultimate survival time that results from this error in calculation are outweighed by the standardization of techniques that can then be made.

[1] T ½ is that time interval in which one half of the transfused cells remain in the peripheral circulation.

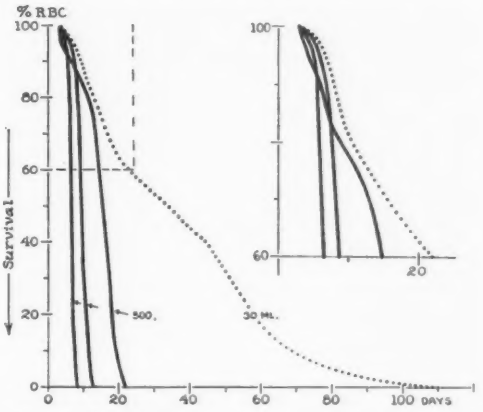

FIG. 3. Erythrocyte survival curves of 4 animals receiving intraperitoneal transfusions from a common donor. The insert indicates the similarity of all of the survival curves during the first several days of the experiments prior to selective removal in 3 animals.

RESULTS

In Figure 1 a summary of the erythrocyte survival curves found in 5 animals trans-

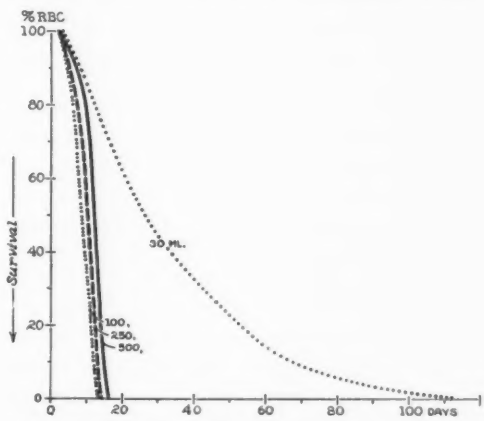

FIG. 4. Erythrocyte survival curves of 4 animals receiving intraperitoneal transfusions in varied volumes from a common donor animal.

TABLE I.—LOCATION OF SEQUESTERED TAGGED ERYTHROCYTES AT POSTMORTEM EXAMINATION OF 2 ANIMALS TRANSFUSED INTRAPERITONEALLY

Organ	*Counts per gram of tissue*	
	Animal 1	*Animal 2*
Spleen	16,200	15,100
Liver	3,760	1,610
Kidney	146	144
Bone marrow	192	100
Lung	34	48
Lymph nodes	4	45

TABLE II.—LOCATION OF SEQUESTERED TAGGED ERYTHROCYTES AT POSTMORTEM EXAMINATION OF 2 ANIMALS TRANSFUSED INTRAVENOUSLY

Organ	*Counts per gram of tissue*	
	Animal 1	*Animal 2*
Spleen	10,300	8,600
Liver	273	448
Kidney	134	178
Bone marrow	86	202
Lung	43	28
Lymph nodes	12	14

fused with 50 milliliters of tagged cells by the intravenous route is shown. The T ½ of this group of animals was 22.0 to 35 days and the ultimate survival time ranged from 96 to 110 days. This is a normal survival time as depicted by the radioactive chromium-tagged erythrocyte technique. The shorter time found as compared to the normal 120 days is due to the fact that small amounts of radioactive chromium are eluted from the red cells during the course of the experiment and this produces a somewhat shortened ultimate survival for these cells, as compared to the Ashby or the radioactive iron techniques.

A summary of the survival curves found in animals transfused intraperitoneally with the same quantity of red cell suspension is presented in Figure 2. The T ½ in this group of animals was 24.3 to 32 days and the ultimate survival was 102 to 110 days.

Despite the small difference in T ½ and ultimate survival found in these curves, no statistically significant difference could be found in the survival time of erythrocytes transfused by either the intravenous or intraperitoneal routes as long as only small quantities of cells were transfused into normovolemic animals. Since the normal survival curve is a steep slope at the onset of the curve, the change in the zero-time value increased the ultimate survival time. These studies indicate that the injection of small quantities of erythrocytes into the peritoneal cavity did not shorten their life span greatly.

Figure 3 is a composite of a group of 4 recipient animals that received intraperitoneal transfusion from the same donor animal. The donor animal was type A positive. One of the recipient animals that received 500 milliliters of tagged cells was type A positive, and 2 of the animals that received 500 milliliters of tagged cells were type A negative. The recipient receiving 30 milliliters of tagged cells was type A negative. Crossmatches and Coombs' tests were negative prior to transfusion. The insert in Figure 3 shows the early part of the survival curve in the 3 animals that received 500 milliliters of tagged blood to be almost identical with the survival curve of the dog that received the 30 milliliters of blood intraperitoneally until 9 to 20 days after transfusion, when each of the animals receiving 500 milliliter transfusions showed the rapid selective removal of the transfused cells from the circulation.

Coombs' tests and crossmatches were negative at this time for the presence of a circulating antibody. Blood urea nitrogen determinations made during this period showed no evidence of renal damage in the experimental animals.

In the series of experiments presented in Figure 4, the blood from the donor animal was common to each of the 4 recipients and was type A negative. The recipient receiving 500 milliliters of tagged cells was type A negative, the recipient receiving 250 milliliters of tagged cells was type A positive, and the recipient receiving 100 milliliters of tagged cells was type A positive. A type A positive received 30 milliliters of tagged cells. As can be seen from Figure 4, a short survival time was produced in the animals receiving 100, 250, and 500 milliliters of tagged cells, whereas a normal survival curve was obtained for the animal which re-

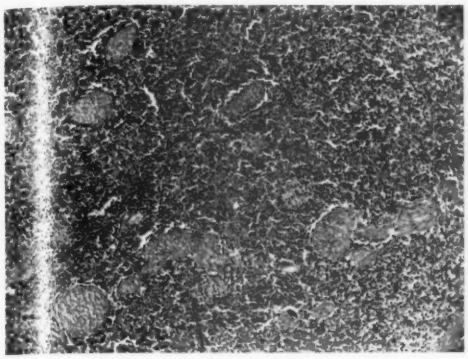

FIG. 5.

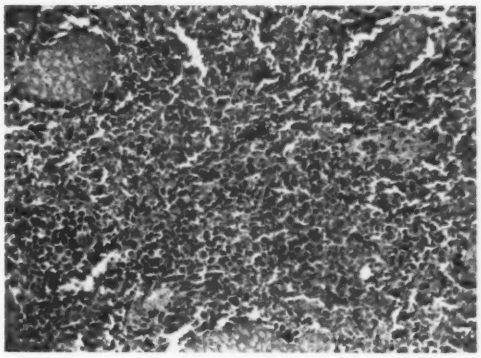

FIG. 6.

FIG. 5. Photomicrograph of a section of the spleen of 1 animal after the selective removal reaction and demonstrating sequestration in splenic sinusoids.
FIG. 6. Same as Figure 5 under greater amplification.

ceived 30 milliliters of tagged cells. All animals were transfused intraperitoneally in this group of experiments.

In a total of 11 animals transfused intraperitoneally, the selective removal phenomenon could be reproduced in all animals receiving 100 milliliters or more of transfused cells. It must be emphasized again that these animals were normal with respect to peripheral circulating hemoglobin concentration at the time of transfusion and, since there had been no recent hemorrhage, were considered normovolemic at the time of transfusion. The phenomenon could not be reproduced in any animal given less than 100 milliliters of tagged cells.

When the selective removal of the transfused erythrocytes had been accomplished and no evidence of radioactivity could be found in the circulating blood, the animals were sacrificed by exsanguination. Samples of various organs of these animals were taken, homogenized, and counted in the well-type of scintillation counter. Table I is an example of the counts per gram of tissue found in 2 animals, the first of which received 500 milliliters of blood intraperitoneally, and the second of which received 250 milliliters of blood intraperitoneally. The highest level of radioactivity in both of these animals and in the remainder of the animals so studied was present in the spleen, with lesser quantities in the liver, kidney, bone marrow, lung, and lymph nodes. The concentration of tagged erythrocytes in the spleen suggests that this organ at least participates in the removal of the major portion of the tagged cells from the blood stream. Whether or not agglutination first occurs and the spleen acts as a sequestration point for these agglutinated cells is open to question, as is the theory that the spleen itself might be responsible for the reaction seen.

Figure 5 is a photomicrograph of the spleen of the animal which received 500 milliliters of radioactive chromium-tagged erythrocytes intraperitoneally after selective removal of these tagged erythrocytes had occurred. In this print and in Figure 6, which is an enlargement of a section of Figure 5, it will be noted that the sinusoids are engorged with erythrocytes and that sequestration is present. The cells appear to be agglutinated in sinusoids in relatively large clumps. In several animals an attempt to produce splenic contracture by injection of 0.5 milliliter of 1 to 1,000 epinephrine intravenously prior to sacrifice produced no apparent re-entry of the tagged cells into the circulation. It is thus apparent that these cells, once removed from the circulation, were no longer available for re-entry, in spite of the fact that the canine spleen will

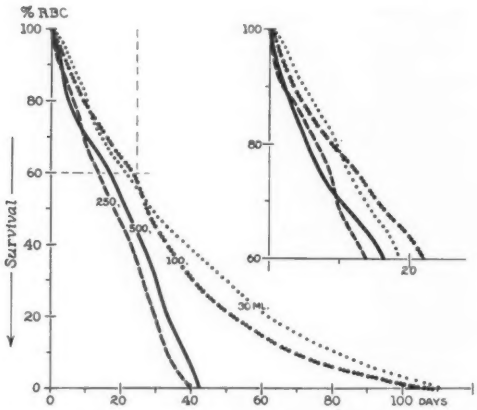

FIG. 7. Erythrocyte survival curves of animals receiving intravenous transfusions of varied volumes of radioactive chromium-tagged cells from a common donor animal. The insert demonstrates the similarity of the initial part of the survival curves in all animals.

contract upon epinephrine stimulation under normal circumstances.

A group of 4 animals was then transfused intravenously with 500, 250, 100, and 30 milliliters of radioactive chromium-tagged erythrocytes from a common donor which was type A positive. The recipients receiving 250 and 100 milliliters of tagged cells were type A positive, whereas the animals which received 500 and 30 milliliters of tagged cells, respectively, were type A negative. The insert in Figure 7 shows a similar survival pattern of the 4 recipients during the early part of the experiment. However, a short survival time was noted in the animals which received 250 and 500 milliliters of tagged cells. This selective removal of the tagged cells occurred at a later time after transfusion, in 38 to 40 days, than in those animals which were transfused intraperitoneally. In addition, the removal from the circulation was accomplished in a more gradual manner. Again, no evidence of change in crossmatch or in the Coombs tests was noted after onset of this reaction. The survival curves of the dogs receiving 100 milliliters and 30 milliliters of tagged cells appeared to be normal.

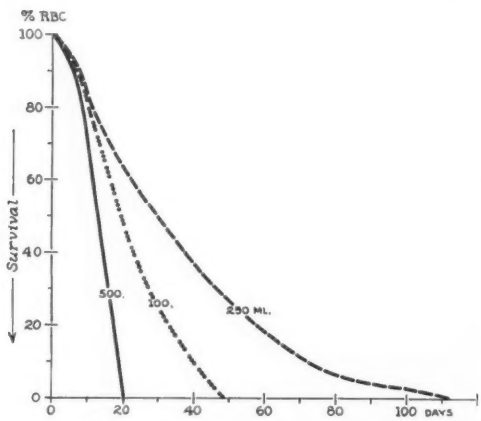

FIG. 8. Erythrocyte survival curves of animals receiving intravenous transfusions of varied volumes of radioactive chromium tagged erythrocytes from a common donor.

Figure 8 shows the survival curve of another group of 3 animals that was transfused intravenously from a type A negative donor. The animal which received 500 milliliters of tagged cells was type A negative, while the other 2 animals were type A positive. In this study, the survival time of the animal transfused with 500 milliliters of tagged cells was 20 days, whereas the animal which received 100 milliliters of tagged cells showed an ultimate survival of 48 days. The animal which received 250 milliliters of tagged cells showed a normal erythrocyte survival time. By comparing the slope of the curve found in the animal receiving 500 milliliters of tagged cells with the pattern of the animals transfused intraperitoneally, there is a marked similarity; but the removal pattern in the animal which received 100 milliliters of tagged cells is very similar to the animals undergoing removal of tagged cells in Figure 7. Fifteen dogs were tested in this way, and the phenomenon of selective removal could be reproduced in about 60 per cent of the animals with volumes of tagged erythrocytes greater than 100 milliliters.

The same type of study of the concentration of radioactivity in various organs that follows selective removal of erythrocytes from the circulating blood stream was carried out in those animals transfused intra-

venously. The relative concentrations of tagged erythrocytes remaining in various organs after removal of these cells from the blood stream were found to be exactly the same as those found in animals transfused intraperitoneally. Table II shows the relative concentration of radioactivity in terms of counts per gram of tissue found in samples of various organs taken from 2 of the animals which had undergone this reaction. In all of the animals studied, no evidence of a circulating antibody could be found by any of the serologic tests that were performed. After removal of the cells from circulation, crossmatches and Coombs' tests were the same as before transfusion. The selective removal of transfused cells from the circulation bore no relation to the blood type of the animal in terms of A positive or negative antigenicity according to Young's grouping.

In order to determine whether a sensitizing effect could be demonstrated by exposing the recipient animals to erythrocyte protein from the donor animal prior to the time of transfusion, 4 animals were first given deep intramuscular injection of 10 milliliters of hemolyzed donor blood on each of 2 occasions 1 week apart, starting 1 month before transfusion. Prior to injection, the donor cells were washed several times with saline in order to be certain that no plasma protein would be present. They were then hemolyzed with sterile distilled water and injected into the recipient animals. After 1 month, the animals were transfused intravenously with 30, 100, 250, and 500 milliliters of donor blood, respectively. The recipients which received 100 or 500 milliliters of blood were type A positive, whereas those receiving 30 and 250 milliliters were type A negative. The donor animal was type A positive. In this group of 4 animals, no change from a normal survival curve could be demonstrated (Fig. 9).

Splenectomy was performed on a group of 4 animals. These animals were then transfused intraperitoneally with 500 milliliters of blood each from a single donor. The blood types of donors and recipients

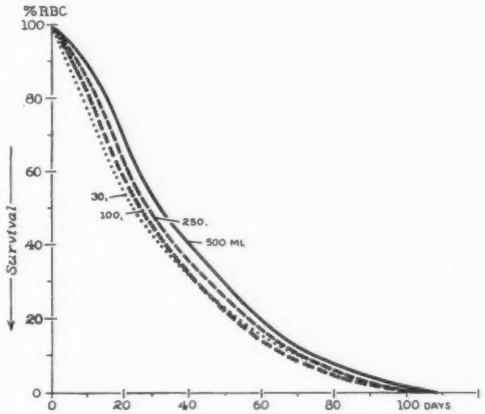

FIG. 9. Erythrocyte survival curves of 4 animals after intravenous transfusion of varied volumes of radioactive chromium-tagged erythrocytes from a common donor. All animals had received previous "sensitization" to donor erythrocyte protein.

were randomized. In Figure 10, the average survival curve for this group is shown. It will be noted that the major variance from the previous studies using intraperitoneal transfusion (Figs. 3 and 4) was the lengthening of the survival curve to an average figure of 43 days; in animals not operated on, the disappearance of the tagged cells from circulation occurred in a period of 9 to

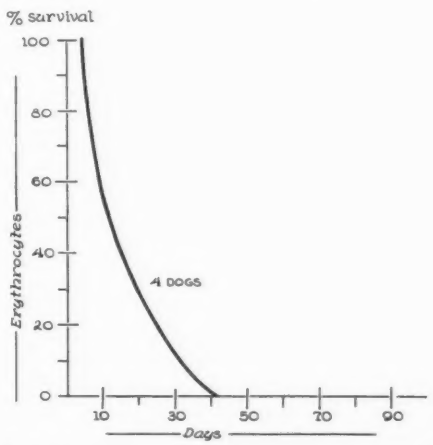

FIG. 10. Average erythrocyte survival curve of 4 animals transfused intraperitoneally with 500 milliliters of radioactive chromium-tagged cells several months after splenectomy.

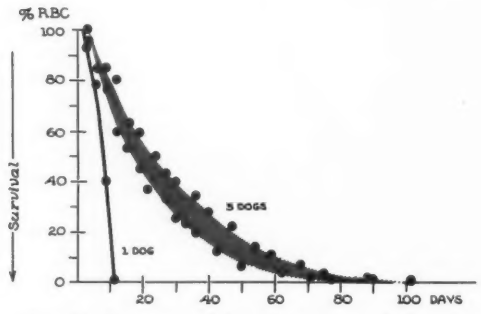

FIG. 11. Summary of 6 erythrocyte survival curves that followed intraperitoneal transfusion of 500 milliliters of donor blood. This study was made within 2 hours after the bleeding of 500 milliliters of blood from each recipient animal.

20 days after intraperitoneal transfusion, again suggesting that the spleen participates in the selective removal reaction.

Figure 11 is a composite of results found in 6 animals which were each bled 500 milliliters prior to receiving 500 milliliters of radioactive chromium-tagged blood intraperitoneally. The animals were each transfused from a different donor and no attempt was made to follow any particular pattern in terms of transfusion with regard to A positive or A negative antigenicity. In 5 of the 6 animals transfused, an approximately normal erythrocyte survival curve was found, and in only 1 animal was selective removal demonstrated with an ultimate survival of the transfused erythrocytes for 12 days. This is in contrast to results obtained after transfusion of a like amount in animals not previously bled; all such animals receiving this quantity of blood intraperitoneally showed selective removal reaction.

DISCUSSION

The selective removal and destruction of apparently compatible tagged erythrocytes follow a pattern which is suggestive of an agglutination type of reaction by nature of the survival curve, but no demonstrable agglutinin could be found by the techniques mentioned. The pattern of shortened survival curves is similar to that reported by Swisher and Young after repeated transfusion of radioactive chromium-tagged erythrocytes, but in that series the reaction was a delayed type which did not occur after a single transfusion. It occurred only after repeated sensitizations with gradually shortening survival times after each subsequent transfusion.

The agglutination type of reaction apparently had no detrimental effect on the experimental animal, and no evidence of renal damage could be detected by measuring the blood urea nitrogen concentrations in the posttransfusion animals. After the hemolytic reaction produced by repeated sensitizations as reported by Swisher, renal damage was noted in some animals.

The difference in the frequency of reaction depending upon the route of transfusion was apparent, but no logical explanation for this can be made at the present time.

The reaction investigated in this report depended, at least to some extent, upon the entrance of large quantities of donor cells into a normovolemic circulation. The transfusion of small quantities or a change from the normovolemic to a hypovolemic state changed the rapidity and the frequency of the reaction. This difference was shown by the markedly decreased frequency of reaction after prior bleeding when only 1 of 6 animals so transfused demonstrated the selective removal reaction. Whether or not this factor is dependent only upon hypovolemia rather than upon decreased red cell mass as well has not been ascertained. The reaction could not be reproduced in any animal receiving a transfusion of less than 100 milliliters of tagged cells, whether the route was by the intravenous or intraperitoneal method.

If the theoretically postulated concept of the selective removal of erythrocytes being an antigen-antibody reaction is correct, then the logical explanation for the lack of reaction with small quantities of donor cells is that the dosage of antigen is insufficiently stimulating to effect a strong titer of antibody production. This possibility could apparently account for the lack of "sensitiza-

tion" produced by prior exposure to donor erythrocyte protein in the amounts used in this study. Factors other than simple protein sensitization are involved, since no change in the frequency of the results could be obtained in the animals transfused intravenously after exposure to the donor erythrocyte protein.

The change in the rapidity of reaction that follows intraperitoneal transfusion in splenectomized animals as well as the variance in frequency, suggests that the spleen is the major site of removal of these cells. Other organs participate to a smaller degree but they could not completely supplant the splenic function in an equivalent period of time. The actual role of the spleen, however, has not been elucidated.

Although the cause of this phenomenon has not been shown, it would seem possible that this experimental preparation would be useful in the further study of some similar human hematologic reactions. Further studies are required in order to elucidate the exact cause of the reaction more fully, but it is suggested, from the nature of the survival curves and the presence of large numbers of agglutinated erythrocytes in the splenic sinusoids, that this was an antigen-antibody reaction conceivably of the agglutinative type. The experimental preparation may also be of value in the study of homeostatic regulatory mechanisms involved in the maintenance of normal blood volumes.

SUMMARY

An experimental preparation which utilizes the transfusion of large volumes of apparently compatible homologous canine erythrocytes and results in the increased destruction and rapid removal of these tagged cells from the circulation is presented. The reaction can be reproduced in 100 per cent of the animals which were transfused intravenously. The reaction apparently bears some relation to the quantity of erythrocytes transfused but bore little relation to prior exposure to red cell protein.

Bleeding to hypovolemic levels immediately prior to infusion decreased the rate of occurrence of the phenomenon.

In all animals in which the reaction occurred, a marked concentration or sequestration of transfused erythrocytes could be noted in the spleen with smaller quantities in various other organs of the body.

The mechanism of this phenomenon remains unknown, although antigen-antibody reactions and the maintenance of normal peripheral circulating hemoglobin and blood volumes may also be involved.

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THE EFFECT OF TOPICAL NITROGEN MUSTARD ON WOUND HEALING

FALLS L. HARRIS, M.D., and COLIN G. THOMAS, JR., M.D., F.A.C.S.,
Chapel Hill, North Carolina

IN THE EXPERIMENTAL ANIMAL the topical administration of nitrogen mustard has proved to be an effective means of controlling the implantation and growth of cancer in surgical wounds. Although tumor cells can frequently be recovered from the wounds of patients undergoing radical cancer surgery, the relationship of these cells to the local recurrence of cancer is by no means clear. Nevertheless, it has seemed logical not only to minimize tumor cell contamination of the surgical wound but also to prevent the implantation of any contaminating cells by an appropriate chemotherapeutic agent. As a consequence topical nitrogen mustard is currently being employed in man as an adjuvant to radical cancer surgery. In the evaluation of any chemotherapeutic agent, not only must its cancerocidal effect be appraised but its effect on wound healing should also be known. This study was undertaken to determine the effects of topical nitrogen mustard in varying concentration on the healing of a standard, experimental surgical wound. As reported previously (8), the concentrations of nitrogen mustard used have in our experience been effective against experimentally implanted cancer.

METHODS

Strain A mice weighing between 20 and 30 grams were anesthetized with 0.5 cubic centimeter of a 3.5 per cent solution of sodium pentobarbital administered intraperitoneally. After the skin had been appropriately prepared with a hexachlorophene soap and shaved, a 3 centimeter incision was made through the skin and panniculus carnosus in the midline overlying the spine. The wounds were then sprayed with 5 cubic centimeters of the appropriate agent. This procedure undermined the skin adjacent to the wound for approximately 1 centimeter. The wounds were then closed with continuous locking sutures of No. 40 stainless steel wire, sutures being placed 8 to 10 millimeters apart. All procedures were carried out under sterile conditions. The animals were weighed on the day of operation. At the end of 8 days the animals were reweighed and sacrificed by cervical fracture. The sutures were removed and the wound and adjacent skin were excised in such a manner as to yield an approximate square of skin 2½ by 2½ centimeters. Cross sections of the wound were taken for histologic study, thereby trimming the length of the wound to exactly 2 centimeters.

The tensile strength of the wound was then measured by placing the tissue between two clamps, the upper being attached to a stationary object, the lower being attached to a plastic plasma bag, hanging free but connected to a source of water flow. Water was then allowed to run into the bag at a constant flow rate until the combined weight of the water plus the bag was enough to disrupt the wound. The weight at which the wound disrupted was regarded as the wound tensile strength.

One hundred and ninety-nine mice, approximately one-half of which were male, were used in this study. The method of

From the Department of Surgery, School of Medicine, University of North Carolina, Chapel Hill.
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TABLE I.—RESULTS IN CONTROL AND TREATED MICE

	Group					
	A .9 per cent saline	*B* 2 mgm. per cent HN_2	*C* 5 mgm. per cent HN_2	*D* 10 mgm. per cent HN_2	*E* 2.5 mgm./kgm. HN_2 intraperitoneally	*F* Protein-deficient starvation diet
No. of mice	42	31	36	37	35	18
Tensile strength, grams*	271.3	235.6	159.0	130.9	257.3	156.6
Standard deviation	78.5	82.5	62.7	38.2	91.0	91.0
Weight in grams*						
Preoperative	22.7	27.0	24.1	25.6	27.3	25.4
Postoperative	23.7	28.6	25.0	25.9	26.1	20.4
Net change	+1.0	+1.6	+0.9	+0.3	−1.3	−5.0
Number of gross wound infections	0	1	1	3	2	1

*Mean for group.

wound management, as well as the number of wounds observed, was as follows: group A, 0.9 per cent saline (controls), 42 wounds; group B, 2 milligrams per cent nitrogen mustard, 31 wounds; group C, 5 milligrams per cent nitrogen mustard, 36 wounds; group D, 10 milligrams per cent nitrogen mustard, 37 wounds; group E, 0.9 per cent saline, followed by 2.5 milligrams per kilogram nitrogen mustard intraperitoneally, 35 wounds; group F, 0.9 per cent saline followed by a protein-depletion diet, 18 wounds. All of these data are shown in Table I.

All of these mice except group F were maintained on a standard laboratory diet, preoperatively and postoperatively. In group F the wounds were irrigated with 0.9 per cent saline after which the mice received 2 grams per mouse per day of a protein-deficient starvation diet, made up of 5 per cent casein, 81 per cent starch, 10 per cent vegetable oil, 4 per cent inert matter, and added vitamins. This diet was in effect during the 8 day period between wounding and sacrifice. Prior to the time of wounding, these mice had been on the standard laboratory diet which was used in animals in the other groups.

Tensile strength studies were carried out 8 days after wounding and treatment. During this period of time, the mice were observed for wound infection, hematoma formation, wound disruption, and general well being.

RESULTS (TABLE I)

Wound tensile strength measured on the eighth postoperative day decreased in a linear fashion as the concentration of nitrogen mustard in the irrigating fluid was increased (Fig. 1). The weight of those animals whose wounds were treated with topical nitrogen mustard was essentially the same as that of the control group. The decrease in tensile strength of groups C, D, and F, when compared to that of the control group A, is significant by statistical study.[1]

Although there was a slight weight decrease in animals receiving intraperitoneal nitrogen mustard, there was no significant decrease in the tensile strength of their wounds. The 18 mice that were placed upon a protein-deficient diet lost approximately 20 per cent of their body weight during the 8 days of observation. Accompanying this weight loss was a 42.5 per cent loss of mean tensile strength of their healing wounds.

A cross section of each wound was examined microscopically and evaluated in terms of fibroblastic response and inflammatory reaction. No gross quantitative

[1]These figures were subjected to statistical study according to the equation of Arley and Buch:

$$t = \frac{\bar{x}_1 - \bar{x}_2}{s\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}}, \qquad s = \sqrt{\frac{f_1 s_1^2 + f_2 s_2^2}{f_1 + f_2}},$$

$$f_1 = n_1 1 - 1, \qquad f_2 = n_2 - 1,$$

t value for group C (5 mgms. per cent HN_2) is 6.9
t value for group D (10 mgms. per cent HN_2) is 9.9
t value for group F (depletion diet) is 4.9
In each instance the value lies outside the .1 per cent limit of probability.

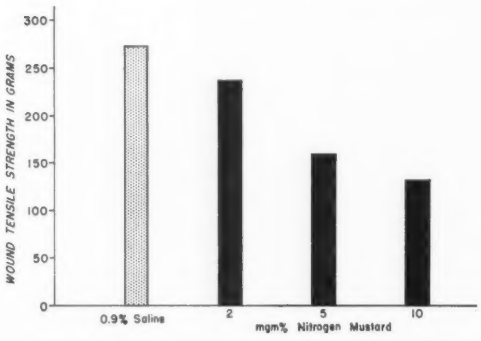

FIG. 1. Determinations on the eighth postoperative day of the tensile strength of wounds in mice after topical administration of varying concentrations of nitrogen mustard.

differences in fibroblastic response were detected when the controls were compared to the treated groups. Microscopically, progressive inflammatory reaction was noted in the 2 milligrams per cent through the 10 milligrams per cent nitrogen mustard treated groups, and the incidence of frank necrosis appeared to be higher in the wounds treated with 10 milligrams per cent topical nitrogen mustard. This finding correlated with the gross observation of no wound infections in the 42 mice in the control group and 7 wound infections in the 139 mice treated with nitrogen mustard.

No hematomas were noted, and there were no wound disruptions.

Activity of the mice operated upon was unremarkable; 24 hours after operation practically all of the mice receiving topical nitrogen mustard exhibited normal activity. The group given nitrogen mustard intraperitoneally were lethargic for more than 48 hours postoperatively, and 5 of 42 died within 24 hours postoperatively.

Figures 2 through 5 are representative photomicrographs depicting typical cellular responses in the control group as well as the groups treated with various concentrations of topical nitrogen mustard. The most striking finding is that of an increasing inflammatory response to increasing concentrations of topical nitrogen mustard. This is characterized by: edema of interstitial and muscle fiber, round cell infiltration, fibrosis, and areas of cellular degeneration varying from karyorrhexis to outright necrosis.

DISCUSSION

Nitrogen mustard (mechlorethamine hydrochloride) is known to have an adverse effect on young proliferating cells; the most likely explanation being the action of the cyclic form of nitrogen mustard on nuclear constituents—the nucleic acids. Observations on the systemic effect of nitrogen mustard on wound healing has given variable results. Conn and associates were unable to detect any decrease in the healing of gastrotomy wounds in dogs; whereas, Farhat and associates noted a decrease in tensile strength of wounds involving skin and panniculus carnosus in rats receiving systemic nitrogen mustard. Hardesty's studies disclosed a loss of tensile strength only when more toxic doses of nitrogen mustard were employed. Since the systemic administration of nitrogen mustard adversely affects several organ systems, it is conceivable that any deleterious influence on wound healing may be a reflection of net body catabolism rather than a specific action on the wound per se. This explanation would seem to be confirmed by the studies of Newsome who was unable to demonstrate any inhibiting influence on wound healing in rats in the absence of weight loss. Farhat also pointed out that the tensile strength loss in wounds of rats following systemic nitrogen mustard was similar to the decrease in tensile strength associated with a starvation diet and comparable loss of body weight.

The only studies of the effect of local chemotherapeutic agents have been those of Hardesty who, without knowledge of concentrations that would be cancerocidal, studied the effect of nitrogen mustard at concentrations of 100, 9, and 5 milligrams per cent. A retardation of 3 days was noted with 100 milligrams per cent solution. With solutions of 9 milligrams per cent, healing

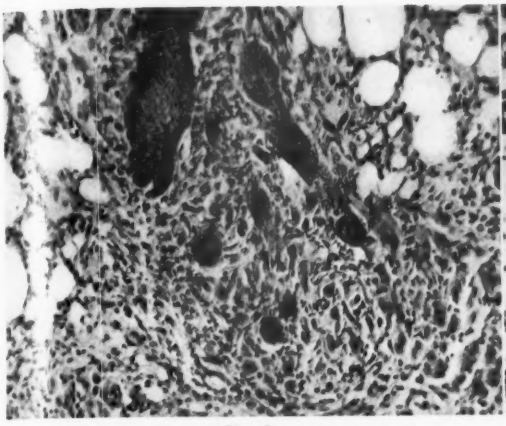

FIG. 2.

FIG. 3.

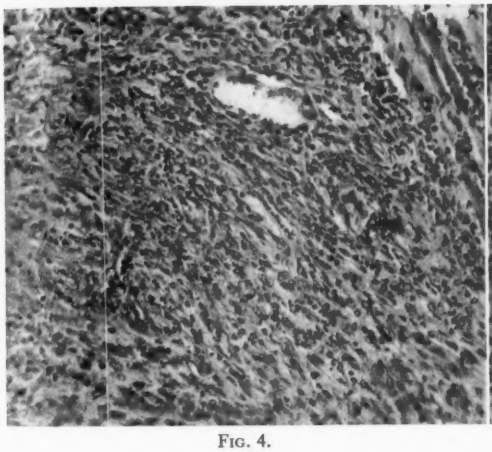

FIG. 4.

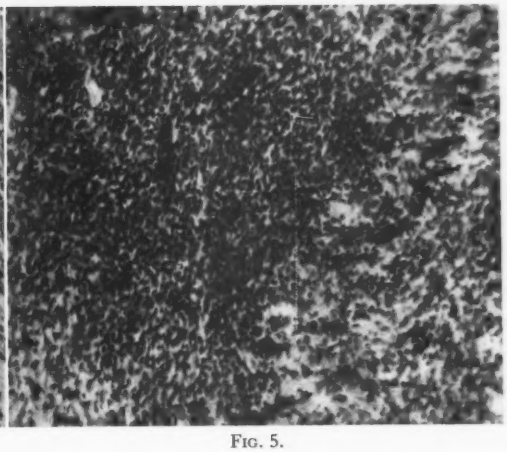

FIG. 5.

FIG. 2. Wound in control animal showing mild inflammatory reaction. Hematoxylin and eosin, × 158.

FIG. 3. Wound in animal treated with 2 milligrams per cent nitrogen mustard shows moderate but well localized inflammatory reaction. There is beginning interstitial muscle edema with round cell infiltration. Hematoxylin and eosin, × 158.

FIG. 4. The effect of 5 milligrams per cent nitrogen mustard is characterized by moderate inflammatory changes with round cell infiltration, interstitial edema, and fibrosis. Hematoxylin and eosin, × 163.

FIG. 5. The effect of 10 milligrams per cent nitrogen mustard is characterized by a more severe widespread inflammatory reaction with abscess formation. Hematoxylin and eosin, × 163.

as measured by tensile strength studies was initially retarded but equal to that in control animals by the ninth day. No differences from the values observed in control animals were noted in wounds treated with 5 milligrams per cent nitrogen mustard. Sections of the wounds in these animals studied histologically were interpreted as showing decreased fibroblastic activity, presumably as a result of the local action of nitrogen mustard "destroying" fibroblasts.

Wound healing is a very complex phenomenon, and although there are many aspects of study, a measurement of tensile strength would seem to be the one best index of normalcy of repair. Harvey and

Edward and Dunphy point to the fibroblast and its activity as the pillar of wound strength. The theory that fibroplasia is inhibited by the nitrogen mustard has been proposed by Farhat and coworkers as an explanation for the decreased wound tensile strength following treatment with nitrogen mustard. Histologic studies, however, have revealed no evidence of wound fibroblastic inhibition following treatment with systemic nitrogen mustard. Microscopic examination of wound cross-sections in the present experiment showed no detectable differences in fibroblastic response when the groups treated with topical nitrogen mustard were compared with the control group. The mechanism of delayed healing and subsequent decreased wound tensile strength is more likely related to the severity of the local tissue injury, requiring a varying degree of phagocytosis and "debris disposal." Such heightened foreign body response is usually associated with delayed fibroplasia and collagen fiber formation. Although these studies do not provide the rate of gain in tensile strength, they do suggest that the normal curve is merely delayed.

Since the topical administration of nitrogen mustard is unassociated with any measurable systemic effect, any adverse effects on wound healing are most likely a manifestation of local injury. The vesicant actions of the mustards are well known and it is probable that any deleterious effects on wound healing are secondary to the relatively nonspecific effects of local injury and an increased inflammatory response. This would be in keeping with the microscopic observations of an increasing inflammatory reaction with increasing concentrations of nitrogen mustard rather than any inhibition of fibroplasia or a specific enzyme inhibition.

In keeping with the nonspecific inflammatory response elicited and the increased susceptibility of such wounds to infection was the slight increase in wound infection.

These studies indicate that the topical use of nitrogen mustard in a concentration of 5 milligrams per cent or greater interfere with normal wound healing in an experimental animal. It is not known, however, whether there is comparable interference in man, in whom of necessity broader surfaces are exposed and local trauma is probably greater.

SUMMARY

A study of the topical effect of varying concentrations of nitrogen mustard, 2, 5, and 10 milligrams per cent, on the tensile strength of healing in experimental wounds in mice indicates a loss of 41 and 52 per cent at 8 days with 5 and 10 milligrams per cent respectively. There was no significant decrease with 2 milligrams per cent nitrogen mustard. The topical use of nitrogen mustard was unassociated with any evidence of systemic effect. Histologic examinations of wounds revealed no evident impairment of fibroplasia but an increasingly severe inflammatory reaction with higher concentrations of the mustard. The adverse effect of topical nitrogen mustard as observed in this experiment is probably on the basis of this nonspecific inflammatory reaction rather than any specific effect on fibroplasia or wound healing per se.

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LEFT BRACHIAL ARTERIAL CATHETERIZATION FOR CHEMOTHERAPY IN ADVANCED INTRA-ABDOMINAL MALIGNANT NEOPLASMS

RALPH L. BYRON, JR., M.D., FELICIANO M. PEREZ, M.D.,
ROBERT H. YONEMOTO, M.D., HOWARD R. BIERMAN, M.D.,
HYMAN L. GILDENHORN, M.D., and KEITH H. KELLY, M.D., Duarte, California

IT IS GENERALLY AGREED that the prevailing chemotherapeutic agents in their usual dose and mode of administration do not greatly alter the course of neoplasms. In isolated instances, particularly of the lymphomas, definite responses such as regression of tumor masses and the relief of symptoms may occur. At present the vigilant search for and ceaseless testing of chemotherapeutic agents are carried out in medical centers throughout the world. A fully effective chemical has not yet been found.

While it is true that an ideal chemotherapeutic agent is wanting, a choice of the available chemicals to be used and the mode of their delivery can be made at this time. Earlier studies (1) have shown that the effect of alkylating agents is greater when they are delivered into the corresponding nutrient artery than when introduced intravenously. It is this basic fact that has encouraged the evolution of various techniques of approach to target arteries. In the early phases, superficially accessible arteries were cannulated with short plastic tubes. The carotids and their branches were used to deliver alkylating agents for tumors of the head and neck, and brachial and femoral arteries for tumors of the extremities. Later, the carotids, the femoral arteries, and the right and left brachial arteries were utilized as portals for catheterizing the aorta and its branches.

From the Department of Oncologic Surgery, Hospital for Tumors and Allied Diseases, City of Hope Medical Center, Duarte.

Double-lumened catheters which have inflatable balloons near their tips, as employed by Watkins and associates, have been designed for entry into the aorta via a peripheral artery and into the vena cava by way of the saphenous vein. These have been used in conjunction with upper thigh pneumatic tourniquets to concentrate the agent in the pelvic area in pelvic malignant lesions without using an extensive laparotomy. Regional and general perfusion techniques with extracorporeal pumps have been developed by Creech and his coworkers to minimize the systemic effects of the alkylating agents yet introduce a much larger dose than is conventionally utilized. However, these perfusions require extensive surgical procedures, extracorporeal apparatuses, general anesthesia, and a highly skilled, specialized team of physicians and technicians. Such perfusions seem to be most useful in lesions of the extremities. Here the escape of the chemical into the general circulation can be largely prevented.

TECHNIQUE

In the past 5 years, a simple and practical method of instilling chemotherapeutic agents into the aorta and its branches through a left brachial artery catheterization technique has been utilized on our surgical service (Fig. 1). This method proved to be safe, simple, and practical. It does not necessitate general anesthesia or laparotomy. This method is the culmination of a series of trials begun on other arteries—the femoral, ca-

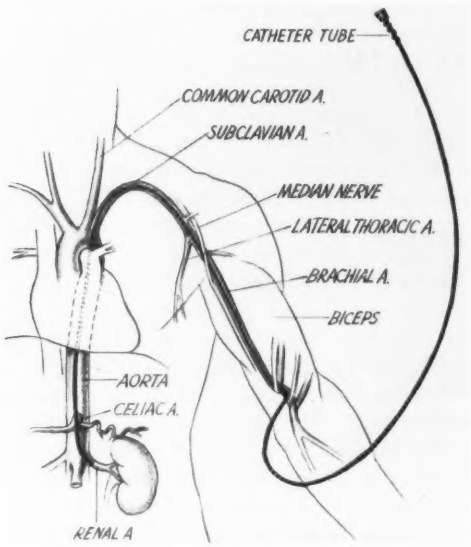


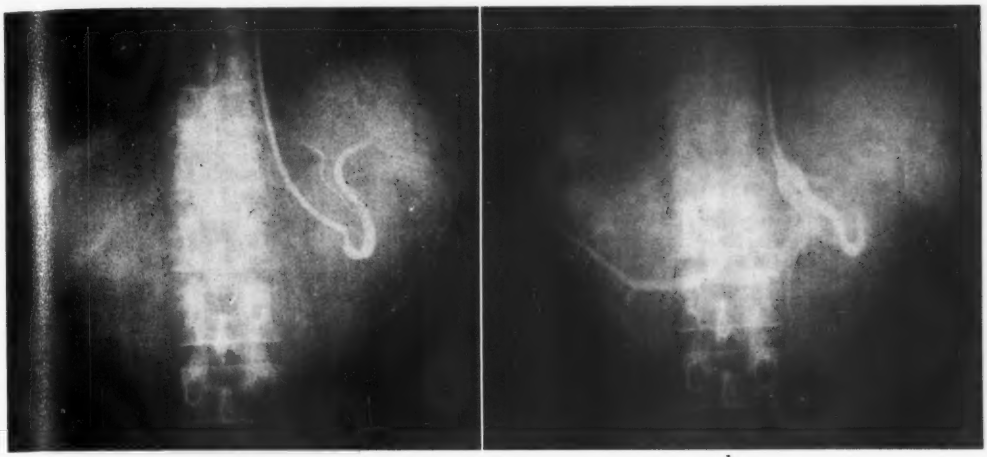
FIG. 1. Diagram of arterial catheterization.

rotid, and the right brachial. The use of these last three mentioned arteries proved to be clinically disappointing. Occasionally, carotid artery catheterization was followed by complications of hemiplegia or hemiparesis due to propagating thrombi or emboli. Because of the configuration of the take-off of the branches of the aorta, these could not be easily catheterized from the femoral artery approach.

The procedure is carried out in the catheterization room by a team of surgeons and roentgenologists. The left brachial artery catheterization is accomplished under routine preoperative medication and local procaine anesthesia. The left brachial artery in its distal one-third below the take-off point of the collateral arteries, the profunda brachii and superior ulnar collateral, is exposed under aseptic conditions and rubber bands are placed around the vessel above and below the site of entry into the artery. A 2 millimeter longitudinal incision is made in the artery and a radiopaque arterial catheter, No. 6 to 10 F., 150 centimeters long, with an 85 degree fixed curve at the tip, is inserted and manipulated into the abdominal aorta and thence into the target artery under fluoroscopic guidance. Contrast medium is instilled into the catheter, and a film is obtained to check the position of the tip and visualize the target viscera roentgenographically. The arterial catheter is filled with heparinized saline, and the fluid is kept running by continuous drip from a reservoir sufficiently high to exceed the aortic systolic pressure. The saline drip is continued until the catheter is removed. After the target artery has been successfully cannulated, the distal brachial artery is ligated and, as such, is "sacrificed." The blood supply to the distal part of the arm is preserved by the intact collateral arteries. The proximal end of the artery is ligated snugly around the catheter to prevent leakage of blood. The skin incision is then closed and the catheter is anchored to the skin. The patient does not have significant postoperative discomfort. He can get in and out of bed, go to a bedside commode, and take his meals with little inconvenience. He may even ambulate up and down the hall, if he takes his saline reservoir with him.

CATHETER REMOVAL

Unlike veins, the arteries show no inflammatory reaction to the presence of the catheter. The arterial catheter is usually left in place for 5 days so that repeated therapy may be carried out. When it is removed, it must be done with the artery exposed, so that the vessel may be ligated proximal to the opening. Removal of the catheter is carried out at the patient's bedside. After local skin preparation and towel draping, the previous wound area is infiltrated with a local anesthetic and the skin sutures are removed. The skin edges are bluntly separated until the brachial artery is exposed. The catheter is then withdrawn gently with a ligature in place ready to be tied around the proximal end of the artery. Previous experience has shown that repairing the arterial defect results in more complications than does simple ligation. The skin is then closed without drainage. Radi-



a b

FIG. 2. a, Before, and, b, after use of adrenalin to force radiopaque medium into hepatic artery without moving catheter.

opaque material can be instilled prior to removal of the catheter to check the position of the tip of the catheter and the possible effects of the therapy.

IMPORTANT POINTS IN THE CATHETERIZATION PROCEDURE

1. The artery must be handled with extreme gentleness in order to avoid spasm. A drop of local anesthetic into the accompanying median nerve is helpful in preventing spasm.

2. As soon as the catheter is inserted into the artery, it should be advanced quickly to the arch of the aorta. There are usually 2 to 3 minutes with the catheter in place before spasm sets in. These are the golden minutes of manipulation of the catheter.

3. Care must be exercised not to allow the catheter to pass down the ascending aorta into the heart. Pressure of the catheter tip on the interventricular septum may be associated with cardiac arrhythmia and even ventricular fibrillation or arrest.

In 1 patient, cardiac standstill developed when the catheter passed down the ascending aorta and entered the heart, producing pressure on the interventricular septum. The catheter was withdrawn, the chest was opened promptly, and the heart was found to be in complete arrest. The heart was successfully started with manual massage and recovery was without complications.

In previous studies it has been observed that pressure by the catheter tip in the septum produces cardiac irregularities which, if the catheter is not withdrawn, may go on to fibrillation or arrest. To avoid this complication, the patient is encouraged to count aloud while the catheter is advanced into the arch. Any interruption in counting suggests an arrhythmia and the need to withdraw the catheter a few centimeters.

After the fluoroscopic control of the catheter tip is undertaken, it is helpful to have the patient in slight left anterior oblique position for the manipulation of the catheter through the arch of the aorta. The tip passes posteriorly when it successfully makes the bend from the arch into the descending aorta.

4. It is helpful for the physician using the catheter to be dark adapted so that he and the roentgenologist may follow the catheter movements under the fluoroscope.

5. The branches of the aorta come off like the branches of a tree and can be best entered coming down the descending aorta.

TABLE I.—TREATED PATIENTS

Patient No.	*Age, yrs.*	*Diagnosis*	*Target artery*	*Chemicals and amt. used*	*Days cath. in*	*Response to treatment*	*Duration of response*	*Complications*	*Survival after treatment, mos.*	*Onset,* mos.*	*Previous treatment*
1	48	Ovarian papillary adenoca. with gen. abdominal carcinomatosis	Aorta	HN_2 30 mgm.	1	Objective improvement	1 mo.	Numbness of left lower extremity, transient	9	13	Complete hysterectomy and irradiation
2	51	Lymphosarcoma retroperitoneal, Hodgkin's type	Celiac axis	HN_2 55 mgm.	1	Marked regression in abdominal mass	21 mo.	None	24	3	Explor. laparotomy. Found inoperable
3	52	Adnoca. rectum, recurrent with metastases	Hepatic artery	HN_2 20 mgm.	1	None	—	Transient labored respiration	8		Explor. laparotomy
4	46	Ca. stomach with liver metastases	Aorta	HN_2 20 mgm.	1	None	—	Upper G.I. bleeding 10 days after treatment	6		Explor. laparotomy
5	48	Abdominal sarcomatosis	Aorta	HN_2 40 mgm.	1	None	—	None	4	5	Explor. laparotomy
6	66	Ca. sigmoid colon with abdominal carcinomatosis	Aorta	HN_2 30 mgm.	1	None	—	None	5	29	Sigmoid resection
7	50	Primary adenoca. of liver	Celiac axis	HN_2 30 mgm.	1	None	—	None	2	13	Explor. laparatomy
8	46	Ca. stomach with hepatic, lymph node, and pancreatic metastases	Hepatic artery	HN_2 60 mgm.	33	None	—	Transient edema of left leg	1		Explor. laparotomy
9	30	Ca. colon with liver metastases	Aorta	HN_2 60 mgm.	2	None	—	None	8	12	Sigmoid resection
10	53	Adenoca. colon with gen. carcinomatosis	Aorta	HN_2 100 mgm.	6	None	—	Slight purpura and edema, both legs	2	24	Explor. laparotomy
11	26	Brest ca. with liver metastases	Hepatic artery	HN_2 120 mgm.	25	Objective regression of liver size	5 mo.	Slight wound skin inflammation	8	13	Rt. breast biopsy, no surgery, x-rays
12†	34	Fibrosarcoma of G.I. origin with gen. sarcomatosis	Aorta and superior mesenteric artery	HN_2 120 mgm.	1	Slow but steady regression	5½ yrs.	None	Living 5½ yrs.	18	Explor. laparotomy, inoperable
13	49	Ca. stomach with gen. carcinomatosis	Celiac axis	HN_2 20 mgm.	2	None	—	None	2 days	4	Partial gastrectomy
14	45	Metastatic hypernephroma	Aorta	HN_2 40 mgm.	4	None	—	None	7	4 yrs.	Left nephrectomy
15	52	Ca. breast with liver metastases	Aorta	Sarcomycin 2 inj.	4	None	—	None	12 days	4½ yrs.	Bilateral radical mastectomy
16	60	Prostatic ca. with liver metastases	Celiac axis	HN_2 90 mgm.	7	40 per cent regression of liver size	2 mo.	None	2½	14	Prostate biopsy and radical prostatectomy
17	66	Ca. sigmoid with liver metastases	Celiac axis	HN_2 30 mgm.	1	None	—	None	3 wks.	9	Sigmoid resection

TABLE I.—TREATED PATIENTS (Continued)

Patient No.	*Age, yrs.*	*Diagnosis*	*Target artery*	*Chemicals and amt. used*	*Days cath. in*	*Response to treatment*	*Duration of response*	*Complications*	*Survival after treatment, mos.*	*Onset,* mos.*	*Previous treatment*
18	60	Ca. transverse colon with abdominal metastases	Celiac axis	HN_2 50 mgm.	4	Subjective improvement	3 mo.	None	Lost to follow-up	24	Transverse colectomy
19	59	Primary hepatic tumor	Celiac axis	HN_2 50 mgm.	9	None	—	Jaundice 3 wks. after treatment	3 wks.	5	Liver biopsy
20	50	Rectosigmoid adenoca. with abdominal metastases	Aorta	HN_2 50 mgm.	5	Pain relief	1 mo.	None	6	22	Sigmoid resection
21	44	Recurrent sarcoma of uterus with abdominal sarcomatosis	Aorta	HN_2 20 mgm.	4	Regression of abdominal mass	10 mo.	None	2 yrs. 4½ mos.	3 yrs.	Explor. laparotomy with HN_2 into aorta
22	63	Ca. rectum recurrent in sacral area	Aorta	HN_2 40 mgm.	3	Pain relief	2 mo.	None	5	6	Abdominoperineal resection
23	35	Adenoca. duodenum involving pancreas	Celiac axis	E-39 830 mgm.	11	Pain relief	2 mo.	Upper G.I. bleeding 3 wks. after treatment	5	2 yrs.	Explor. laparotomy
24	54	Ca. urinary bladder with pelvic metastases	Aorta	E-39 600 mgm.	11	None	—	None	15 days	3 yrs.	TUR
25	8	Wilms' with gen. abd. and pulm. metastases	Celiac axis	E-39 200 mgm.	6	Marked regression in liver size	3 mos.	Radial & median nerve weakness, alopecia, hemodepression, marked	7½	10	Nephrectomy and irradiation
26	35	Ca. rectum with abdominal carcinomatosis	Aorta	E-39 480 mgm.	13	Pain relief	16 days	Hematuria, melena, skin petechiae 3 wks. after treat.	23 days	3 yrs.	Abdominoperineal resection
27	47	Ca. colon with hepatic metastases	Celiac axis	HN_2 50 mgm.	2	None	—	None	2	16	Colon resection
28	44	Ca. colon with hepatic metastases	Aorta	HN_2 30 mgm.	3	Transient subjective relief	—	None	5 wks.	2½ yrs.	Palliative resection of colon
29	53	Ca. pancreas with hepatic metastases	Hepatic	HN_2 60 mgm.	3	None	—	None	9 wks.	2 wks.	Explor. laparotomy
30	54	Ca. rectum, recurrent with gen. abdominal carcinomatosis	Aorta	HN_2 60 mgm.	3	Pain relief	1 mo.	None	4½ mos.	3	Abdominoperineal resection
31	60	Ca. pancreas with hepatic metastases	Celiac axis	HN_2 60 mgm.	3	None	—	None	8	2 yrs.	Explor. laparotomy
32	66	Ca. ovary, recurrent with abdominal metastases	Aorta	HN_2 20 mgm.	1	None	—	None	5	7 yrs.	Oophorectomy
33	53	Ca. rectum, transitional cell	Hepatic	HN_2 40 mgm. with adrenalin	3	Objective improvement in liver	7 mos.	G.I. bleeding	Living 3 10 mos.	yrs.	Abdominoperineal resection
34	65	Ca. rectosigmoid with pelvic metastases	Aorta	E-39 700 mgm. Sarcomycin 136 mgm.	25	Temporary relief of severe pain	—	None	27 days	14	Sigmoid resection

TABLE I.—TREATED PATIENTS (Continued)

Patient No.	*Age, yrs.*	*Diagnosis*	*Target artery*	*Chemicals and amt. used*	*Days cath. in*	*Response to treatment*	*Duration of response*	*Complications*	*Survival after treatment, mos.*	*Onset,* mos.*	*Previous Treatment*
35†	39	Adenoca. sigmoid with hepatic metastases	Hepatic	HN_2 40 mgm. Myleran 20 mgm.	3	Liver size regression	—	None	18	2½ yrs.	Sigmoid resection
36	44	Adenoca. rectosigmoid with hepatic metastases	Hepatic	HN_2 40 mgm. Myleran 15 mgm.	3	Clinically objective	8 mos.	None	15	1 yr.	Sigmoid resection
37	50	Leiomyosarcoma rt. kidney with extensive regional infiltration	Rt. renal artery	HN_2 40 mgm. Myleran 20 mgm.	8	None	—	None	3	13	Rt. lumbar exploratory
38	38	Breast ca. with abd. carcinomatosis	Celiac axis	HN_2 40 mgm. Myleran 20 mgm.	4	Clinically objective	15 mos.	Two grand mal convulsions	Living 22 mos.	4¾ yrs.	Rad. mastectomy, adrenalectomy, and subtotal gastrectomy
39	49	Ca. urinary bladder with pelvic metastases	Aorta	HN_2 40 mgm. Myleran 20 mgm.	4	None	—	None	12 days	4 yrs.	TUR

*Onset—from first surgical procedure and biopsy.
†Patients 12 and 35 had 2 catheterizations with marked improvement in Patient 12 after the second procedure.

6. The celiac artery comes off the aorta anteriorly about 5 centimeters below the medial crux of the diaphragm. As the catheter enters the celiac axis it makes a sharp bend.

7. In contrast to the celiac artery, the renal arteries come off laterally and the catheter follows a gentle sweeping curve as it enters the renal artery. When the catheter tip enters the renal artery, the operator is immediately oriented. The celiac artery will arise 2 to 3 centimeters higher than the renal and more anteriorly. As the catheter is withdrawn from the renal artery it is rotated and then advanced into the celiac artery.

8. Injection of an opaque medium and taking a spot roentgenogram are of aid in better orientation and prove the position of the catheter tip.

MATERIAL AND METHOD

Forty-four subjects underwent this procedure. Of this number, 39 had successful catheterization and administration of chemotherapy. The 5 untreated patients consisted of the 4 or 9 per cent of patients in whom unsuccessful attempts at catheterization were made and 1 patient for whom diagnostic contrast medium visualization of the abdominal viscera was carried out. The lesions consisted of various combinations of hepatic, general abdominal, periaortic nodal, and pelvic metastases of abdominal and retroperitoneal visceral origin. The patients had advanced malignant lesions and were beyond definitive surgical or irradiation therapy. Seventeen of the 39 patients treated had pathologic identification of the metastases immediately before the catheterization. The remaining patients had had biopsies at previous laparotomies. In 3 cases, the breast was the origin of the lesion. Four subjects had pulmonary metastases and 2 had bone involvement as well as intra-abdominal tumor. Two patients were treated in a preterminal state in an attempt to palliate the severe pain.

Of the 39 patients treated, the tip of the catheter was placed in the aorta just below the diaphragmatic level in 19 cases, in the celiac axis in 12, in the hepatic artery in 7, and in the right renal artery in 1. Five patients had subsequent courses of chemo-

therapy through other avenues of approach. Two had second catheterizations.

Aside from the instillation of the chemotherapeutic agents, the catheter was utilized to administer whole blood and plasma, electrolytes, analgesics, and nutritional adjuvants. In conjunction with the therapy, contrast medium visualization of the arteries and viscera as well as the study of histamine and adrenalin effects on neoplastic arterial supply were made in selected patients.

It has been noted previously that an extensive independent arterial supply develops in neoplastic masses. These newly developed nutrient arterioles appear to react differently physiologically as compared with normal arterioles, perhaps because of the lack of innervation. The direct histamine instillations do not cause dilatation, and adrenalin administration does not cause constriction of tumor arterioles, although neighboring arterioles supplying normal tissue react normally. This lack of vascular response to adrenalin can occasionally be utilized selectively to increase the amount of chemical reaching the tumor or to drive the chemotherapy into the proper nutrient artery (Fig. 2).

CHEMOTHERAPEUTIC AGENTS USED, METHOD OF INSTILLATION, AND RESULTS

There were 33 instillations of nitrogen mustard in total doses of 20 to 140 milligrams; 5 instillations of 5 to 30 milligrams of myleran; 5 of 200 to 830 milligrams of E-39, and 3 of sarcomycin.

Group 1. Single doses of nitrogen mustard ranging from 20 to 55 milligrams with the application of arterial tourniquets to both upper thighs were employed. The catheter was usually removed at once after the drug administration. Of 7 patients so treated 2 had objective improvement and 5 had no objective or subjective improvement.

Group 2. Multiple doses of one chemotherapeutic agent, either nitrogen mustard, E-39, myleran, or sarcomycin, were instilled. It was noted that the arterial catheter could be kept open and in place up to 25 days without untoward sequelae. This is in marked contrast to venous catheters which usually produce marked reaction in 1 to 4 days. Of the 26 patients in this group, 21 received nitrogen mustard. Six patients had objective improvement, 7 had moderate relief of pain, and 13 had no objective or subjective relief. E-39 was used in 4 cases. One patient had regression of liver metastases and 1 relief of symptoms. Sarcomycin was used in 1 case with no clinical improvement.

Group 3. Alternating doses of chemotherapeutic agents instilled every 8 hours were used in 6 cases. The purpose of this alternating chemotherapy was to observe possible summation of the effect of different chemotherapeutic agents which have their action on different phases of cell division. Nitrogen mustard, 10 milligrams every 16 hours, and myleran, 5 milligrams every 16 hours, were used in 5 cases. Three patients had objective improvement. A patient treated with E-39 alternating with sarcomycin showed temporary relief of severe pain but no objective changes.

COMPLICATIONS OF CHEMOTHERAPEUTICS

Immediate effects on instillation included 2 separate episodes of grand mal convulsive seizures which occurred during administration of nitrogen mustard and myleran alternately in 1 patient.

Delayed effects included the following reactions. One patient had transient numbness of the left lower extremity 2 weeks after the second dose of 10 milligrams of nitrogen mustard but recovered completely. There were 3 cases of gastrointestinal hemorrhage. Bleeding occurred from the upper part of the tract 10 days after administration of 20 milligrams of nitrogen mustard but responded to conservative treatment. Bleeding from the same source occurred 3 weeks after administration of E-39 in a total dose of 830 milligrams. The packed cell volume was 19 per cent, the white blood count was 130, and platelets, 94,000 at the start of hemorrhage. With intensive supportive care, the patient recovered in 10 days. Gastrointes-

tinal bleeding occurred after administration of 40 milligrams of nitrogen mustard into the hepatic artery.

There was transient edema and purpura of both lower legs after administration of 100 milligrams of nitrogen mustard. Jaundice and signs of hepatic insufficiency occurred in a patient with massive metastases 3 weeks after therapy. Hematuria, melena, and skin petechiae were noted 3 weeks after administration of 480 milligrams of E-39. The packed cell volume was 22 per cent, the white blood count was 400, and platelets, 14,000.

Four patients, 10 per cent, died within 15 days. In 11, 28 per cent, there was objective improvement, average survival 19.1 months, and 3 patients still living. Subjective improvement was noted in 8, 21 per cent, with an average survival 3⅓ months.

DISCUSSION

The intra-arterial catheter makes possible the arterial administration of chemotherapy in poor risk patients. It is simple, practical, and associated with low mortality and morbidity. It makes possible the delivery of one or more chemicals in high concentration to the tumor areas. A series of treatments can be administered while the catheter is still in place. In addition to the more intensive local action of the chemotherapy, the systemic effects appear to be somewhat less than with equivalent doses intravenously. Because of the tendency for adrenalin to constrict normal vessels and not those supplying the tumor, the effect of the chemical on the tumor may be further enhanced in selected cases by preceding the chemical with adrenalin. Whether this is a worthwhile procedure in any individual case is determined by studying the vascular pattern with an opaque medium before and after adrenalin administration.

When the metastases are primarily in the liver, the introduction of the chemical into the hepatic artery enables the liver metastases to be reached selectively, since almost 100 per cent of the blood supply to the tumor is from the hepatic artery. In contrast, the liver parenchyma gets only about 15 per cent of its blood supply from the hepatic artery and 85 per cent from the portal vein. Liver function studies confirm that while tumor nodules are decreasing in size, the liver function remains essentially unchanged.

As more and more chemotherapeutic agents become available, it should be possible to select chemicals that act on different phases of cell division. Our combinations of chemotherapy are an attempt at this; alkylating agents are thought to act on the metaphase, dimethyl myleran may have its effect somewhat earlier in the cycle. This basic principle should have increasing usefulness as the exact mode and place of action of chemicals become better understood.

The arterial administration of chemicals via a catheter to the blood supply of a tumor appears to have certain advantages over the limited perfusion technique of Creech. It is simple and requires no costly equipment or specialized teams. It permits high, concentrated dosage with chemotherapy which may be repeated daily. It is inferior to the perfusion technique by allowing a higher percentage of the chemical to enter the systemic circulation.

SUMMARY

Experience with intra-arterial catheterization as a mode of administration of chemotherapy and a description of the left brachial artery technique are presented. The results suggest that further evaluation and study are warranted. The brachial artery can be ligated safely in its lower third.

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TOTAL RED CELL VOLUME CHANGES ASSOCIATED WITH EXTENSIVE SURGERY

ROBERT C. HOYE, M.D., ALFRED S. KETCHAM, M.D., and
NATHANIEL I. BERLIN, M.D., Bethesda, Maryland

THERE ARE MANY REPORTS dealing with the measurement and replacement of blood lost during surgery but few have dealt with the changes in blood volume which may occur in the postoperative period. Stewart and Rourke demonstrated that the postoperative changes in blood and interstitial fluid were greater than could be accounted for by the loss from the operative wound. A study by Storey and associates on patients undergoing pulmonary resection showed that 40 per cent of the measured blood lost was not replaced during surgery. McInnes and associates noted in 4 patients that postoperatively the blood and the total red cell volumes tended to decrease unless transfusions were given. Berlin and co-workers (3) and Royster and associates suggested that the blood volume turnover following thoracic or head and neck surgery was greater than usually measured at the operating table. Parsons has discussed the indication for blood volume determinations in extensive surgical procedures. Topley and Clarke, using red cells labeled with radioactive phosphorus in patients after trauma, found the average decrease of total red blood volume to be 11 per cent in the posttraumatic period.

The present study was designed to measure the loss of red blood cells during both the operation and the postoperative phase in patients undergoing extensive surgery. This investigation was further designed to demonstrate blood loss which is not usually measured in the operating room and also to introduce a simple method for its determination.

From the Surgery Branch and General Medicine Branch of the National Cancer Institute, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare, Bethesda.

METHOD

Total red cell volume (TRCV) determinations, using sodium chromate containing radioactive chromium, were made immediately preoperatively, immediately postoperatively, and on the second and fourteenth postoperative days by a modification of the technique described by Read. The samples were counted in a well type scintillation counter using a single channel gamma ray spectrometer. All samples were measured to a counting error of ± 1 per cent. The entire technique as used in this study gave an average difference of 1.5 per cent, 0 to 4 per cent, in 5 control subjects having duplicate determinations made several days apart.

The turnover, i.e., loss, of red blood cells was calculated from the difference in two red blood cell volume determinations plus 200 cubic centimeters per unit of blood for each transfusion given. For the purpose of comparison the total red cell volume loss has been converted to whole blood loss by dividing by the average hematocrit during the interval studied.

Blood loss at surgery was measured by the automatic conductivity bridge technique as described by LeVeen and Rubricus. A 2.5 per cent mannitol solution was used for moistening sponges and pads. In addition to the measurement of blood on sponges, laparotomy pads, towels, and via suction, all drapes and gowns were measured for blood content in the latter part of the study. It was shown that 200 cubic centimeters of

TABLE I.—TOTAL RED CELL VOLUME IMMEDIATELY PREOPERATIVELY AND POSTOPERATIVELY

Patient No.	Sex	Age, yrs.	Operation	TRCV Calculated Normal c.c.	TRCV Preop. c.c.	RBC's replaced at operation* c.c.	TRCV Postop. c.c.	Turnover at operation Total RBC c.c.	Turnover at operation RBC c.c./kgm.
1	F	48	Total pelvic exenteration	1450	1559	1000	1347	1212	20.9
2	F	52	Total pelvic exenteration	1450	1396	800	1166	1030	17.8
3	F	64	Total pelvic exenteration	1550	1288	1400	1544	1144	18.5
4	M	48	Laryngectomy rad. neck diss.	1200	1257	1000	1114	1143	28.6
5	F	37	Radical hysterectomy	1350	1603	1400	1485	1518	28.1
6	F	46	Ant. pelvic exenteration	1850	1163	1200	1411	952	12.9
7	F	56	Ant. pelvic exenteration	1575	982	2600	817	2765	43.9
8	F	44	Ant. pelvic exenteration	1725	1828	1400	1206	2022	29.3
9	M	64	Rad. excision pelvic tumor	2730	2487	2600	1693	3394	37.3
10	M	41	Parotidectomy rad. neck diss.	2370	1509	1200	1360	1149	14.5
11	M	49	Laryngectomy rad. neck diss.	2310	1967	600	1991	576	7.5
12	F	51	Post. pelvic exenteration	1200	1306	1400	1097	1609	33.5
13	F	39	Radical hysterectomy	1500	1292	1800	1352	1740	29.0
14	F	62	Mandibulectomy rad. neck diss.	1375	1619	2000	1117	2502	45.5
15	M	64	Hemipelvectomy	1728	1506	1200	1541	1165	20.1
16	F	34	Radical hysterectomy	1600	1319	800	1308	811	12.7

*200 c.c. RBC contained in 500 c.c. whole blood.

whole blood poured onto a surgical drape would record a loss of approximately 200 cubic centimeters when the blood-stained portion of the drape was placed into the machine for 3 to 5 minutes of manual agitation and thorough wringing out.

The patients were selected at random from a series of patients scheduled to undergo radical surgery. No patient was in clinical shock or receiving blood at the time of the determination. All were adequately hydrated. The usual physical signs and tests were used as indicators for blood transfusion. Postoperative wound drainage was of the character and quality usually associated with the surgical procedures carried out.

The normal total red cell volume for each patient was calculated from the patient's stated average normal weight and by using 30 cubic centimeter per kilogram for males and 25 cubic centimeters per kilogram for females. No patient in the study had received a blood transfusion within the month previous to surgery.

RESULTS

Tables I, II, and III list the data obtained by measurement and calculation for each of the patients in the study. Table I shows that in 10 of the 16 patients studied there was a failure to replace the blood lost at surgery, varying up to 794 cubic centimeters of red cells. In 3 instances there was in addition to replacement, a net gain up to 256 cubic centimeters, and in 3 instances no significant change occurred. The total red cell volume turnover varied from 576 cubic centimeters to 3,394 cubic centimeters. This loss has also been shown in terms of cubic centimeters per kilogram of body weight, so that a comparison can be made of the total red cell loss without consideration of differences in body weight.

TABLE II.—OPERATIVE WHOLE BLOOD LOSS

Patient No.	Measured loss*: Suction, sponges c.c.	Measured loss*: Gowns, drapes c.c.	Measured loss Blood volume determinations c.c.	Deficit in unreplaced whole blood† c.c.	Per cent of total loss
1	1700	(.)	3030	−1330	44
2	1650	(.)	2341	− 691	30
3	2200	(.)	2571	− 371	14
4	2200	(.)	3307	−1107	33
5	2800	(.)	3750	− 950	25
6	2000	(.)	2375	− 375	16
7	6000	(.)	7900	−1900	24
8	3700	(.)	4878	−1178	24
9	4900	(.)	7600	−2700	36
10	2100	1050	2985	+ 165	5
11	950	350	1369	− 69	5
12	2200	1150	3575	− 225	6
13	3800	645	4193	+ 252	6
14	4100	1465	6029	− 464	8
15	1800	1285	2949	+ 136	5
16	1500	655	2205	− 50	2

*Measured on automatic conductivity blood loss meter.
(.) This loss was not measured in the first 9 patients studied.
†Deficit in unreplaced whole blood is the difference between loss measured from TRCV determinations and blood measured in suction, sponges, gowns, and drapes.
Column 3—(columns 1 and 2) = column 4.

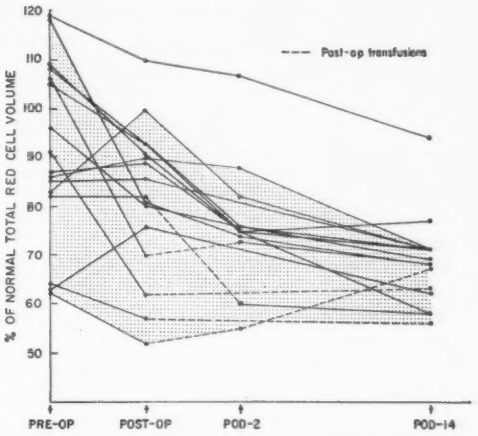

FIG. 1. Per cent of normal total red cell volume present in 16 patients before and after radical surgery.

Table II shows the blood loss on the drapes and gowns to range from 350 cubic centimeters to 1,465 cubic centimeters and indicates the necessity of including all blood lost in the determination of operative blood loss. In 9 patients, when only the laparotomy pads, sponges, and suction were measured, there was a deficit in unreplaced whole blood of 371 cubic centimeters to 2,700 cubic centimeters. In the remaining 7 patients, the drapes and gowns were also measured and the unreplaced blood loss varied from −464 cubic centimeters to +252 cubic centimeters of whole blood. The loss measured in drapes and gowns accounted for one-seventh to one-third of the total blood loss.

Table III shows that an additional decrease in total red blood cell volume in the postoperative period varied from 160 cubic centimeters to 477 cubic centimeters. In the last column of Table III this additional loss is compared to the total red cell volume immediately postoperatively and is shown to represent a 9 per cent to 44 per cent decrease in total circulating red cell volume. Fifteen of the 16 patients were anemic by blood volume standards by the fourteenth postoperative day (Fig. 1).

The hematocrit was an unreliable guide in assessing changes in the patient's blood volume. In Table IV are data from 6 of the 11 patients who were not transfused postoperatively. An average red cell loss of 370 cubic centimeters in 3 patients during the 14 day postoperative period was reflected in a hematocrit change of only 4 to 6. Yet 3 other patients having a smaller average loss of 209 cubic centimeters of cells had an average hematocrit change of 13.

DISCUSSION

In a previous study (2) it was found that the total red cell volume is often decreased in patients with cancer. In the patients studied in this series the total red cell volume on admission was not determined. The clinical status and the peripheral blood counts were used as indicators for preoperative transfusion which was reflected in the immediate preoperative total red cell volume determination as much as 38 per cent less than calculated normal.

The loss of blood during surgical operation has been measured by many investigators using various techniques, and an

TABLE III.—RED BLOOD CELLS LOST IN THE POSTOPERATIVE PERIOD

Patient No.	Postoperative TRCV Immed. c.c.	Postoperative TRCV Day 2 c.c.	Postoperative TRCV Day 14 c.c.	c.c. of RBC transfused postop.	RBC loss First 2 days c.c.	RBC loss Day 2 to 14 c.c.	Total	Per cent postop. TRCV loss in 2 weeks*
1	1347	1095	1035	0	250	62	312	23
2	1166	1116	1000	0	50	116	166	14
3	1544	1276	1099	0	268	177	445	29
4	1114	901	919	0	213	18	195	18
5	1485	1448	1266	0	40	179	219	15
6	1411		1144	0			267	19
7	817	866	1056	600	151	210	361	44
8	1206	1257	1170	400	350	86	436	36
9	1693		1732	200			160	9
10	1360		1330	200			230	17
11	1991		1640	0			351	18
12	1097	898	694	0	200	203	403	37
13	1352	1321	1070	0	31	251	282	21
14	1117	1014	930	0	103	84	187	17
15	1541	1300	1227	0	241	73	314	20
16	1308	965	931	100	423	54	477	36

*RBC loss × 100 ÷ postoperative TRCV.

TABLE IV.—EXAMPLES OF THE FALLACY OF RELYING ON THE POSTOPERATIVE HEMATOCRIT DETERMINATIONS

Patient No.	Normal TRCV c.c.	Operation	Immediately postop. TRCV c.c.	Immediately postop. Hct.	14th day postop. TRCV c.c.	14th day postop. Hct.	Total 14 day change in TRCV c.c.	Total 14 day change in Hct.
3	1550	Total exenteration	1544	49	1099	43	445	6
15	1728	Hemipelvectomy	1541	40	1227	35	314	5
11	2310	Larynx and neck	1991	43	1640	39	351	4
Av.	1863		1692		1322		370	5
2	1450	Total exenteration	1166	46	1000	31	166	15
6	1850	Ant. exenteration	1411	46	1144	32	267	14
4	1200	Larynx and neck	1114	42	919	32	195	10
Av.	1500		1230		1021		209	13

attempt has been made to arrive at an average figure for each type of operative procedure. Bonica and Tyler have reviewed this material and conclude that all of the investigators agree that the blood loss at operation is always greater than the anticipated or estimated loss. Baronofsky and others have emphasized the advantages of frequent measurements of blood lost during the course of long operations and of blood replacement made accordingly. The present study has demonstrated that if accurate replacement is to be achieved, all of the sites of external loss must be measured. In 7 patients selected at random the blood on the drapes was considerably in excess of the loss as estimated by the surgeon and comprised from 15 to 42 per cent of the total operative loss. The value of knowing the total loss as it occurs is obvious in patients losing from 5 to 15 units of blood during a 4 to 8 hour surgical procedure. With the use of the conductivity bridge technique the measurement of this lost blood is simple and accurate if that on the gowns and drapes is measured.

Of equal importance to the loss which occurs in the operating room is that which occurs postoperatively (Table III). This loss occurs insidiously and will frequently remain unrecognized unless the total red cell volume is measured. In this study the loss has varied from 9 to 44 per cent and averaged 22 per cent of the immediate postoperative total red cell volume. Part of this loss undoubtedly is due to the continued seepage of blood at the drain site, but other processes must also be responsible. Stanton, Prentice, Canham, and Topley and their co-workers have described similar postoperative red blood cell losses. Stanton and as-

sociates have stated that this loss may be as much as twice the operative loss and that it could not be adequately explained by compensatory plasma dilution, decreased blood formation, or changes in the mean corpuscular volume of the red blood cells. In 57 patients with trauma, Topley demonstrated an average decrease of 11 per cent of the total red cell volume in the period from 4 to 14 days after trauma. This decrease was probably not due to decreased erythrocyte production, since reticulocyte counts were 4 to 5 per cent. Davies and Fisher found that decreased activity and bed rest could account for 4 to 5 per cent of this decrease. Other suggestions include the hemolysis of transfused cells, the sequestration of blood, and reflex vasodilatation producing blood pooling. The best explanation, however, is probably the continued leakage of blood into tissues about the operative site.

The fallacy of assuming a quantitative relationship between the postoperative hemoglobin or hematocrit and changes in the blood volume was demonstrated in 1938 by Stewart and Rourke. Since then it has been repeatedly demonstrated that there is no strict parallelism between the changes in the hemoglobin concentration or the hematocrit and those in the total red cell volume.

SUMMARY

1. The changes in the total red cell volume and the blood volume loss in 16 patients undergoing radical surgery for cancer are presented.

2. From 15 to 42 per cent of the surgical blood loss is on the drapes and gowns.

3. After radical surgery the insidious loss of red blood cells in the postoperative period may equal the operative loss. In this study it represented from 9 to 44 per cent of the total red cell volume present immediately postoperatively.

4. The postoperative hematocrit is a convenient but unreliable guide in assessing the further postoperative loss of red blood cells.

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NEUROLOGIC COMPLICATIONS OF FRACTURES AND DISLOCATIONS OF THE PELVIS

F. P. PATTERSON, M.D., F.R.C.S.(C)., F.A.C.S., and K. S. MORTON, M.D., F.R.C.S.(C)., Vancouver, British Columbia, Canada

NERVE INJURY as a result of fracture of the pelvis is an entity rarely discussed and, at most, briefly referred to in standard textbooks on fractures and joint injuries. Our attention was drawn to this injury when we were confronted, in the short space of 1 year, with 5 such cases. A search of the records of the Vancouver General Hospital over the years 1950 to 1959 inclusive revealed an additional 5 cases, and increased awareness of this possible defect detected a further 5 cases in the first 6 months of 1960. These 15 cases, with some interesting observations on 1 similar case, are the basis of this report.

The literature on this subject has been unusually limited. In 1936, Lam made the statement that nerve injury in fracture of the pelvis is probably more common than is generally recognized and we believe this statement holds today. Lam presented 9 cases of nerve damage, and from the previous 20 years' literature was able to find 14 cases in 1,889 fractures reported. Thus his own incidence in 100 fractures was 9 per cent while that in the literature was 0.75 per cent.

Since that date no article in the English literature has been devoted to nerve injury in fractures of the pelvis. Greene and Smith review Lam's conclusions but mention no cases of their own. Conwell records an incidence of 4 per cent "sciatic nerve injuries" in 185 fractures of the pelvis, based on Noland and Conwell's review in 1933. Carruthers and Logue mention having encountered 3 cases of obturator nerve injury but do not present any details. Urist reports 1 case of obstetric fracture-dislocation of the pelvis with first sacral and fifth lumbar root involvement. Dommisse mentions 1 case with associated lesion of first, second, and third sacral roots.

Bonnin, however, develops a point of interest implicating fracture of the sacrum as responsible for cauda equina injury in association with fracture of the pelvis. He points out that fracture of the sacrum is frequently missed in these cases, a point appreciated by Wakeley, Mendelmann, and Furey. Bonnin found that in 45 per cent of fractures of the pelvis there were fractures of the sacrum as well; Wakeley's incidence was 4 per cent; Furey's was 74 per cent. In the present series, sacral fractures were recognized in 5 of 15 cases—33 per cent.

Perrazini, in a review of 81 fractures of the pelvis, found 9 cases in which nerve compression was noted—12 per cent. These involved mainly the sciatic nerve. Junge reviewed the literature and quoted incidence figures of 0.41 per cent, 0.66 per cent, and 0.75 per cent in large series. He included several isolated reports in small series, and the impression is gained that recovery was excellent.

DISCUSSION OF CASES

It is apparent that the initiating trauma is severe, 10 of 15 patients being pinned or crushed for a time under heavy machinery (Table I). Of the remaining five, 1 was struck by a heavy object, 1 was involved in a high speed auto accident, 2 were pedestri-

From the Trauma Research Unit, Deparument of Surgery, University of British Columbia and the Vancouver General Hospital, Vancouver.

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TABLE I.—SUMMARY OF CASES

Case Age, years Sex	Mechanism of injury	Initial examination	Roentgenology
1 39 M	Pelvis crushed between two logs	No motor weakness, 3½ mos.; atrophy right thigh and calf; sensation normal; right ankle reflex absent	Undisplaced fracture left superior and right inferior pubic rami; 5th lumbar root sleeve absent right
2 25 M	Pinned by heavy motor across back and left leg	Weak dorsi and plantar flexion, hamstrings and quadriceps with atrophy left thigh and calf, 3 mos. Diminished sensation lateral side left calf and foot. Diminished left ankle reflex	Displaced fracture left superior pubic ramus involving acetabulum. Separated symphysis. Fractured right sacral body. Subluxation left sacroiliac joint
3 54 M	Fell 30 feet	Weak dorsi flexion left foot. Diminished sensation dorsomedial aspect left foot. Ankle reflexes absent bilaterally	Displaced fracture left pubic rami; fracture left wing of sacrum
4 25 M	Pinned by tanker truck	Absent dorsiflexion, plantar flexion and eversion left foot. Hyperesthesia over entire foot and lower half left leg. Deep reflexes normal	Fracture right pubic rami and wing of ilium with displacement and shortening. Separated symphysis
5 23 M	Struck by a log	"Left foot drop"	Fracture left acetabulum with central dislocation. Fracture body of right pubis. Separated symphysis
6 6 F	Truck wheel ran over pelvis	Weak dorsiflexion left foot. Sensation and reflexes normal	Separated symphysis; subluxated sacroiliac joints. Fracture left iliac crest
7 26 M	Two ton loading machine rolled onto pelvis	Bilateral loss of dorsiflexion at ankles. Hyperesthesia L5 and S1 dermatomes bilaterally. Ankle reflexes absent bilaterally	Undisplaced fractures of both left and right pubic rami. Subluxation of sacroiliac joint with fracture of iliac wing
8 32 M	Pinned by a truck turned over on him	Weak dorsiflexion left foot, 4 mos. Marked atrophy left thigh and calf. Decreased sensation posterior thigh, absent sensation dorsolateral aspect left foot. Left ankle reflex depressed. Loss of urinary bladder control	Bilateral fractures of pubic rami with moderate displacement
9 28 M	Pinned by 4 ton donkey engine	No motor power distal to left hip; weak glutei and left hip flexors. Absent sensation lateral aspect left leg and foot	Fracture right pubic rami; slight displacement of symphysis. Subluxation of left sacroiliac joint
10 65 M	Crushed between truck and logs	Left Trendelenburg, 10 mos. Atrophy and weakness left glutei. Deep reflexes and sensation normal	Fracture left pubic rami. Subluxation left sacroiliac joint. Fracture 5th sacral segment
11 66 M	Struck by a car	Loss of sensation right below knee. Bilateral loss of ankle reflex. "Right sciatic palsy"	Fracture right acetabulum and ischiopubic junction. Fracture left pubic body and ischiopubic junction. Fracture right wing of sacrum
12 31 M	Pinned under caterpillar tractor	Weak left hip flexors, quadriceps and muscles of the leg. Loss of sensation in lateral femoral cutaneous nerve distribution bilaterally. Hyperesthesia right sole; absent sensation left buttock	Fracture left superior pubic ramus. Subluxation right sacroiliac joint. Separated symphysis pubis. Fracture of third sacral segment
13 35 M	Passenger in auto accident	Absent left hamstrings, calf and leg muscles. Absent sensation left sole, paresthesia lateral left leg. Absent left ankle jerk	Fracture left acetabular floor with central dislocation. Subluxation left sacroiliac joint. Fracture right pubic rami
14 53 F	Struck by a car	Weak right hip adductors, confirmed later by electrical examination. Marked weakness of right hip abductors and flexors, slight weakness of right quadriceps	Comminuted fracture right innominate with gross central displacement of femoral head. Comminuted fractures of right pubic rami and body
15 20 F	Struck by a car	A "flicker" of movement in left hip adductors noted, 3 mos. Other thigh and leg muscles and sensation previously recorded as normal	Comminuted fracture of left innominate bone with minimal central displacement of femoral head. Comminuted fracture of left pubic rami. Subluxation of left sacroiliac joint
16 22 M	Crushed between two trucks	Flexor spasms and clonus right lower extremity. Hyperesthesia right leg and foot. Right ankle reflex absent	Fracture four pubic rami. Failure of left 5th lumbar root sleeve to fill on myelogram

ans hit by cars, and 1 fell 30 feet. All but 3 were male, and 10 of the 15 were in their third or fourth decades. Fractures suffered were correspondingly severe, with the pelvic ring continuity broken anteriorly and posteriorly in 12 of 15 cases.

Outstanding is the inadequate record of neurologic findings in all cases. In 4 instances a satisfactory examination was recorded only several months after injury and in a fifth, the only early record was of a "left foot-drop." This fault undoubtedly reflects an unwillingness to record findings on hospital charts but almost certainly also indicates a failure to expect and detect the neurologic defect. Lam and Perrazini also remarked on this delay in recording the neurologic findings and believed it represented a true late development of palsy.

An additional case (Case 16) is included because of its similarity and because operative findings were of interest in determining the level of the lesion. The myelographic changes led to exploration of the involved fifth lumbar root but no disease of the disc could be found. Some spastic elements in the neurologic examination in this case suggested cord damage rather than more distal nerve damage.

In 2 other cases surgical exploration was performed. In Case 10, with gluteal muscle weakness, an attempt was made to expose the superior gluteal nerve but this was abandoned when a mass of scar tissue was encountered in the region of the greater sciatic notch and venous bleeding became alarming. Open reduction of the acetabular fracture in Case 13 revealed the sciatic nerve to be stretched over the major displaced fragment and impregnated with a number of small bony fragments.

LEVEL OF THE LESION

It unfortunately appears to have become a habit to refer loosely to any peripheral nerve lesion in the lower extremity as a "sciatic nerve palsy," especially if weak dorsiflexion of the foot is observed. Certainly with fracture-dislocation of the hip the description is accurate since the sciatic nerve is the only trunk partially or completely involved. In pelvic fractures and dislocations, however, it is clearly not so. In Cases 2, 8, 9, 10, 12, 13, and 14 it is apparent that sciatic, femoral, gluteal, posterior cutaneous, lateral femoral cutaneous, and obturator nerves can be damaged.

That such widely spread nerve trunk damage is possible is favored by the mechanism of injury in 10 of 15 cases: pinning or crushing of the lower trunk and upper thigh by heavy objects could, by pressure, involve a number of nerve trunks in this area. Certainly, in Case 13, more direct damage to the sciatic nerve trunk by bony fragments and fracture displacement was proved at operation.

On the other hand, the site of damage might be more localized if lumbar and sacral root or plexus damage were postulated. In Case 16 it was thought that involvement of the fifth lumbar root was proved but this could not be confirmed at operation and, certainly, the completeness of the paralysis in some cases, e.g., Case 9, would argue against root damage.

Perhaps a more satisfactory explanation of the lesion is, therefore, damage at the plexus level. Clinical detail in these cases does not warrant any firm conclusions in this regard but it is clear that the lumbosacral trunk, carrying fourth and fifth lumbar roots to the sacral plexus, is not exclusively involved. This trunk has been implicated by Urist, by Lam, and by Davis (quoted by Lam). Because of its proximity to the posterior pelvic ring fracture or dislocation and the frequent involvement of muscles dependent on its roots, it is likely that the lumbosacral trunk is commonly involved. Case 14 is of interest in this regard with involvement of hip adductors (obturator nerve, second, third, and fourth lumbar roots), hip abductors (gluteal nerves, fourth and fifth lumbar, first and second sacral roots) and hip flexors (femoral nerve, second, third, and fourth lumbar roots; and

TABLE II.—PROGNOSIS IN 10 CASES

Case No.	*Follow-up period*	*Result*
1	7½ mos.	Tires easily; pain right hip; right limp; ¾ in. wasting right thigh; 1 in. right calf; right ankle reflex absent. Return to same work as scaler with 15 per cent disability
2	2 yrs. 6 mos.	Weak dorsiflexion left foot. Hypesthesia lateral aspect left calf. Left ankle reflex absent. Return to lighter work as service station operator with 5 per cent disability
3	1 yr. 8 mos.	Moderate wasting left buttock with Trendelenburg. Weak left ankle dorsiflexion, hamstrings, hip abductors and extensors. Hypesthesia left lateral leg and foot. Bilateral absent ankle reflexes. Part-time return to same work as longshoreman with disability
4	9 mos.	Low back pain with left sciatica. Weak left anterior tibial and peroneal muscles. Paresthesias lateral aspect dorsum left foot. Return to same work as truck driver with no disability
5	1 yr. 8 mos.	Left hip arthrodesis. Weak left anterior tibial and peroneal muscles. Hypesthesia lateral aspect left calf and dorsum of foot. Change of work from logger to watchmaker with 60 per cent disability
6	1 yr. 2 mos.	Slight weakness of left anterior tibial muscle. Left ankle reflex depressed. Student. No disability
7	3 yrs. 9 mos.	Bilateral weakness of hamstrings and gluteus maximus; absent dorsiflexion of ankles, weak plantar flexion and peronei. Paresthesias lateral aspect left leg. Right ankle reflex normal, left absent. Change of work from truck driver to bookkeeper with 75 per cent disability
8	1 yr. 3 mos.	1 in. wasting left calf; tibialis anterior and posterior and extensor hallucis longus rated 3–4. Hyperesthesias of toes and outer border left sole. Left ankle reflex absent. Currently under treatment for urinary incontinence
9	1 yr. 3 mos.	Slight left limp and drop-foot gait; 2¾ in. atrophy left thigh, 1 in. left calf. Weak left tibialis anterior. Sensation normal. Bilateral absent ankle reflexes; left knee reflex depressed. Return to same work as logger with 15 per cent disability
10	2 yrs. 2 mos.	Left Trendelenburg; gluteal atrophy; no gluteal power. Deep reflexes normal. Retired with 50 per cent disability

directly from lumbar roots). This combination of weaknesses could be explained most easily by damage at the lumbar root level but most likely by damage at the nerve trunk level because of the proximity of the obturator and femoral nerves and the lumbosacral trunk at the superior limit of the sacroiliac joint. Lumbosacral trunk involvement alone would not, however, explain the frequent involvement of the first sacral root as indicated by sensory defect and loss of ankle reflex (Cases 1, 2, 3, 7, 8, 9, and 11), nor of the obvious femoral nerve distribution involved in Case 9.

One further observation is of interest in regard to the level of the lesion. Urinary incontinence in Case 8—and possibly also Case 3—indicated involvement of fourth and fifth sacral roots. Bonnin has suggested that this lesion is related to sacral fracture with cauda equina injury. In Case 8, no sacral fracture could be identified on roentgenographic examination.

INCIDENCE OF COMPLICATIONS

Ten of these cases appeared within a 10 year period during which time there were 809 admissions for fracture of the pelvis. Thus the incidence of nerve injury in this series is 1.2 per cent. This figure is close to twice that of Lam's quoted figure of 0.75 per cent. In a somewhat longer period of time, 62 traumatic hip dislocations with sciatic nerve lesions in at least 16 per cent were recorded (12). The incidence of nerve injury in fractured pelvis is, therefore, much lower than in hip dislocation, but, because of the greater number of fractures of the pelvis encountered, the actual number of nerve lesions presenting as problems is somewhat similar in the two injuries.

Relating other complications of fractures of the pelvis to these incidence figures, Moore (10), in a review of 1,307 pelvic fractures in 10 years, encountered 25 intestinal perforations, 15 liver injuries, and 7 splenic injuries for a total incidence of 3.6 per cent. In the same series (11) he also reported 3 ruptured diaphragms and 13 vascular injuries—1 per cent. Genitourinary injuries, however, remained the chief complication with 104 patients suffering 122 injuries—9.3 per cent. These figures included contusions of a degree to cause

concern. Lam's figure for genitourinary complications in 1,468 cases was 11 per cent.

PROGNOSIS

Ten patients have been followed up sufficiently long to warrant some conclusions as to prognosis (Table II). Firstly, results in 6 could be considered good in that final percentage disability was small and the original heavy occupation was returned to. One remains under treatment for persistent urinary incontinence, the result of nerve injury, and the remaining 3 have poor results with 50, 60, and 75 per cent disability. In 1 of these a hip arthrodesis contributed to the disability rating and in another, age—67 years—was a factor.

Considering the neurologic lesion itself, however, in none did complete recovery occur. In 7, ankle jerks remained absent; in 9, muscle weakness or paralysis was recorded; and in 7 an appropriate area of hypesthesia or hyperesthesia persisted. Length of follow-up ranged from 7½ months to 3 years 9 months, or an average of 1 year 6 months.

SUMMARY AND CONCLUSIONS

1. Fifteen cases of fracture-dislocation of the pelvis with neurologic complications have been reviewed and 1 similar case of interest has been reported. The sparse literature on this subject has been reviewed.

2. Neurologic complications of fracture-dislocation of the pelvis are frequently undiagnosed, principally because of a lack of awareness of the possibility of nerve damage and because they are obscured by the associated severe bony and soft tissue injury.

3. The level and site of the nerve lesion would seem to vary. With fracture of the sacrum and with bladder disturbances the root level is indicated; with marked hemipelvic displacement one suspects lumbar or sacral plexus damage, particularly the lumbosacral trunk; in some cases direct pressure on nerve trunks seems to be the best explanation of the defect.

4. Nerve damage in pelvic injury is less common than genitourinary and visceral damage and about equal in incidence to vascular damage. Figures herein reported reveal that it is as great a clinical problem as sciatic nerve injury in dislocation of the hips.

5. The over-all functional results of this injury are good, 7 of 10 patients returning to heavy work with only slight compensable disability. Restoration of the neurologic defect is, however, never complete.

6. A plea is made for a greater awareness of this injury and for more complete and careful neurologic assessment at the time of injury.

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THE EFFECT OF 6-MERCAPTOPURINE ON RENAL HOMOGRAFT SURVIVAL IN THE DOG

C. F. ZUKOSKI, M.D., H. M. LEE, M.D., and D. M. HUME, M.D., F.A.C.S.,
Richmond, Virginia

ALTHOUGH the mechanism of homograft immunity is not completely defined, some combination of serum antibody with circulating lymphoid cells capable of transferring homograft immunity is generally accepted as the instrument causing the destruction of the homografted tissue by the host. Attempts have been made to suppress antibody formation and thus prolong homograft survival by the use of radiation, nitrogen mustard, cortisone, and recently purine antagonists, and other substances have been studied.

Schwartz, Eisner, and Dameshek (12) were able to show that the purine analogue 6-mercaptopurine (6-MP) could alter antibody formation to soluble protein antigens in such a way as to allow the development of temporary tolerance in the adult animal. Meeker and associates (8) were able to demonstrate prolongation of skin homograft survival in rabbits given relatively large daily doses of 6-MP, but no prolongation was noted in mice (7). Schwartz and Dameshek (11) found that 6-MP could prolong rabbit skin homografts. Hubay and associates, however, were unable to demonstrate prolongation of skin homograft survival in mice, rats, guinea pigs, or rabbits receiving the test substance, 6-mercaptopurine.

The present study was undertaken to investigate the effect of 6-MP on renal homograft survival in the dog. A preliminary report of this work has already been published (14).

From the Department of Surgery, and the Surgical Research Laboratories, Medical College of Virginia, Richmond.
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METHODS

Adult mongrel dogs weighing 10 to 25 kilograms were used in all experiments. Renal transplants were exchanged between animals of the same sex in all instances. The 6-MP was administered intravenously once a day through a polyethylene catheter in the external jugular vein, and the first dose was given just prior to the renal transplantation.

The animals were divided into 5 groups. In the first 2 groups, the right kidney was removed, and the renal homotransplant was placed in the right renal fossa by a method previously described (5). The ureter was brought out to the skin to permit an accurate collection of urine through a catheter tied into the ureter. When the function of the transplant was prolonged, the tip of the ureter usually sloughed, and the cannula had to be replaced so that ultimately pyelonephritis resulted. Under these circumstances, the microscopic appearance of the transplanted kidney was sometimes obscured by an ascending infection. In this group of animals, the 6-MP was administered in doses of 5 to 10 milligrams per kilogram per day until the homograft ceased to function or until the animal died. These large doses produced anorexia, vomiting, diarrhea, jaundice, and eventual death in many instances.

In the last 3 groups of animals, the kidney transplant was placed in the pelvis and the ureter was anastomosed to the bladder. The renal artery and vein were anastomosed end-to-end with the common iliac vessels. The animal was then bilaterally nephrectomized and the function of the homotrans-

TABLE I.—SUMMARY OF 6-MP DOGS IN THIS STUDY

Dog No.	*Day of last normal B.U.N.*	*Secreting period,* days*	*Survival time, days*	*B.U.N. at death†*
GROUP I—UNILATERAL NEPHRECTOMY AND 10 MGM. 6-MP/KGM./DAY REGIMEN				
1		5	9, sacrificed	
2		9	9, died	
3		5	9, sacrificed	
5		6	9, sacrificed	
GROUP II—UNILATERAL NEPHRECTOMY AND 5 MGM. 6-MP/KGM./DAY REGIMEN				
8		6	9, sacrificed	
9		4	6, sacrificed	
10		14	14, died	
11		19‡	22, died	
12		14‡	14, died	
13		16‡	18, died	
16		15	15, died	
17		15	15, died	
GROUP III—BILATERAL NEPHRECTOMY PLUS 5 MGM. 6-MP/KGM./DAY REGIMEN				
19	15	19		200
20	13	15		200
23	4	17		200
25	66	66		15
26	22	35		230
27	10	29		108 (21 days)
28	2	20		200
31	—	17		300
44	8	12		180
45	11	13		20
46	42	42		20
47	7	30		200
49	8	20		160
51	—	12		120
52	14	16		30
53	17	19		15
54	—	12		105
57	31	32		15
GROUP IV—BILATERAL NEPHRECTOMY PLUS 3 MGM. 6-MP/KGM./DAY REGIMEN				
29	—	8		55
33	5	25		240
34	35	35		25
38	11	12		25
39	3	7		130
40	—	9		120
41	—	22		200
GROUP V—BILATERAL NEPHRECTOMY PLUS 2.5 MGM. 6-MP/KGM./DAY REGIMEN				
35	—	7		—
36	4	15		300
37	3	23		340

*Number of days secreting 50 c.c. per day or more clear urine.
†B.U.N. last recorded, usually within 3 days of death.
‡The 6-MP was stopped on the fourteenth day. In all other instances the 6-MP was given until death.

plant was estimated by the level of blood urea nitrogen, the survival of the animal, and, whenever possible, by the observation that the animal was continuing to pass urine. These 3 groups of animals were similarly handled except for the dosage of the 6-MP: (a) 18 dogs received 5 milligrams per kilogram per day for 4 to 9 days, followed by 2.5 milligrams per kilogram 2 out of 3 days thereafter; (b) 7 animals received 3 milligrams per kilogram per day for 4 days, then 2 milligrams per kilogram 2 days out of 3, while 1 additional animal received 2 milligrams per kilogram every other day; (c) 3 dogs received 2.5 milligrams per kilogram per day. These groups will be characterized hereafter as the 5, 3, and 2.5 milligram regimen.

TABLE II.—SURVIVAL

Procedure	*No. of dogs*	*Postoperative survival, days* Average	Range
Bilateral nephrectomy alone	4	7.5	7–8
Bilateral nephrectomy with renal homotransplantation	10	15.0	9–25
Bilateral nephrectomy with renal homotransplantation plus 6-MP 5 mgm./kgm. regimen	18	23.7*	12–66
Average function† of canine renal homografts	150	5.9	2–14

*p value less than 0.05 when compared with group with bilateral nephrectomy and renal homotransplantation.
†Based on a minimum of 50 c.c. urine output per day.

In addition to these experimental groups, 2 groups of control experiments were performed. In the first set, the animals were bilaterally nephrectomized and observed until death. In the second set, the animals were bilaterally nephrectomized and a renal homograft was placed in the pelvis with the ureter anastomosed to the bladder. The animals were given no 6-MP but were observed until death.

All animals received a clysis or intravenous infusion of 1,000 cubic centimeters of 5 per cent dextrose in water or 5 per cent dextrose in saline daily throughout the duration of the experiment.

RESULTS

The results of the 6-MP experiments are tabulated in Table I as follows:

Group I. Four dogs received 10 milligrams per kilogram per day of 6-MP. One animal (dog 2) died on the ninth day of therapy still excreting urine, and the other 3 (dogs 1, 3 and 5) were sacrificed on the ninth day. All 4 demonstrated an early homograft reaction microscopically.

Group II. Eight dogs received 5 milligrams per kilogram per day. The renal homograft in 6 of these dogs functioned for 14 days or longer. Two of these 6 animals (dogs 13 and 10) died at 18 and 14 days, one of them showing an early homograft reaction microscopically and the other appearing to be normal. In a third (dog 11), the homograft was normal at biopsy on the fourteenth day at which time the 6-MP was stopped. At death 8 days later, the kidney transplant was enlarged and showed severe infection microscopically. A fourth (dog 12) showed marked enlargement grossly, and microscopically, a severe pyelonephritis. A fifth and sixth (dogs 16 and 17) died on the fifteenth day of 6-MP administration at which time no homograft reaction was apparent either grossly or microscopically. The other 2 (dogs 8 and 9) showed typical homograft reactions when sacrificed on the ninth and sixth days, respectively.

Group III. Of 18 bilaterally nephrectomized animals receiving the 5 milligrams per kilogram 6-MP regimen, 8 had prolonged survival of 20 days or more. The average survival time was 23.7 days. Six of the 18 dogs (dogs 45, 52, 53, 57, 46, and 25) died at 13, 16, 19, 32, 42, and 66 days with a normal blood, urea nitrogen, whereas the remaining 12 dogs maintained a normal blood urea nitrogen for an average of 9 days but all 12 ultimately died with an elevated blood urea nitrogen. The survival of this group is compared with that of the control group in Table II.

Group IV. Seven dogs received the 3 milligrams per kilogram 6-MP regimen and survived for an average of 16.7 days (range 7 to 35 days). Two animals (dogs 38 and 34) died with a normal blood urea nitrogen on the twelfth and thirty-fifth days.

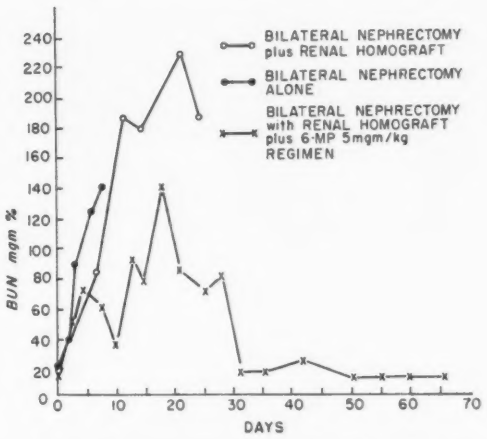


FIG. 1. Points represent averages of the blood urea nitrogen for the number of dogs surviving and having determinations on these dates.

Group V. Three dogs were given the 2.5 milligrams per kilogram 6-MP regimen and survived an average of 15 days (range 7 to 23 days). All animals in this group had an elevated blood urea nitrogen after the fourth day.

Controls. In the control groups, 4 bilaterally nephrectomized animals lived an average of 7.5 days (range 7 to 8 days). Ten animals were bilaterally nephrectomized and received a pelvic renal homotransplant without any 6-MP administration. These animals survived an average of 15.0 days (range 9 to 25 days), and no animal had a normal blood urea nitrogen past the eighth day. (Fig. 1 and Table II). In 2 experiments in which the animal was bilaterally neprectomized with a homografted kidney in the pelvis, the ureter was anastomosed to the bladder in the usual way and a cannula was placed in the bladder for urine collection. These transplants functioned satisfactorily for an average period of 5.9 days.

Grossly the renal homotransplant in the 6-MP treated animals showed much less edema and enlargement at postmortem examination than was the case with the nontreated animals. In those experimental animals dying with a normal blood urea nitro-

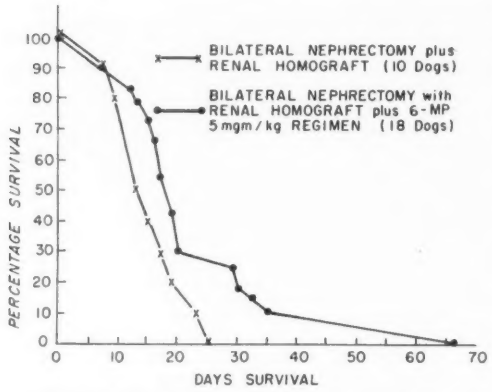


FIG. 2. Comparison of the daily and percentage survival of the bilateral nephrectomy plus renal homograft dogs and the bilateral nephrectomy with renal homograft plus 6-MP 5 milligrams per kilogram regimen.

gen the kidney was of normal size. The cut surface of renal homotransplant in the 6-MP animals was sometimes completely normal in appearance and at other times had small hemorrhagic areas. The gross appearance of a normal kidney, a renal homotransplant control, and the renal homotransplant of dog 25 which survived for 66 days are compared in Figure 3.

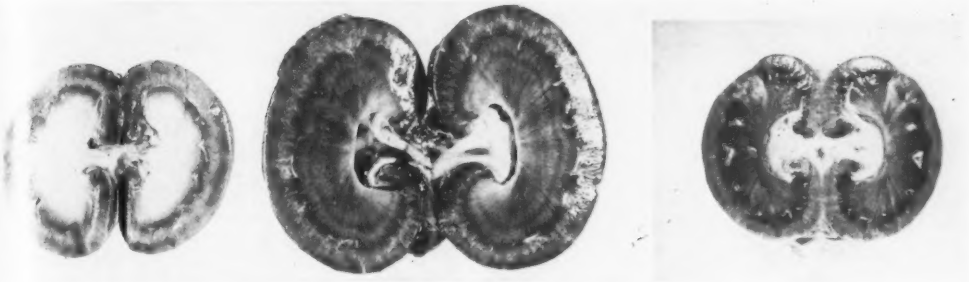
Microscopically, the homograft reaction in the untreated animals is characterized by interstitial edema, round cell infiltration of the interstitial tissue by lymphocytes of host origin, tubular destruction, and often areas of hemorrhage. As the reaction progresses there is damage to the walls of the smaller blood vessels with piling up of lymphocytic cells within the lumina of the vessels, followed ultimately by thrombosis of the vessel and infarction of that portion of the kidney supplied by the vessel. This reaction is illustrated in Figure 4. Microscopically, the renal homografts in the 6-MP treated animals show much less round cell infiltration and edema than the untreated animals. The microscopic appearance of the homograft in the 6-MP treated animal which functioned for 35 days (dog 34) is shown in Figure 5. Biopsy of the renal homograft in dog 25 which functioned for 66 days was performed on the thirtieth day (Fig. 6). It may be seen that there is a moderate perivascular and periglomerular round cell infiltration, but rather good preservation of the tubules. By the sixty-sixth day this infiltration had been replaced in some areas by extensive fibrosis and tubular destruction associated with mild round cell infiltration as shown in Figure 7. In other areas of this homograft there was a relatively more normal renal cortex (Fig. 8) with distinctly less round cell infiltration than had been present in the earlier biopsy (Fig. 6).

The destructive action of 6-MP on rapidly proliferating cells is demonstrated in the mesenteric lymph nodes of the dogs receiving this drug for protracted periods of time. A normal mesenteric lymph node is shown in Figure 9, while one from dog 34 receiving 6-MP over a 35 day period is shown in Figure 10. The 6-MP treated lymph nodes had a marked loss of central lymphoid tissue with an almost total loss of follicles at the periphery of the nodes, though concentrations of lymphoid tissue remained in most of the nodes subcapsularly. The loss of lymphoid tissue in both areas of the node appeared more marked with the prolongation of 6-MP therapy.

It was necessary to continue to administer the 6-MP throughout the course of the animal's survival, for its withdrawal at any time (even after 30 days of therapy) was followed by rejection of the homograft.

Prior to the transplantation there was no way of predicting whether or not prolonged function would follow 6-MP administration. However, during the course of the experiment an elevation of the blood urea nitrogen usually suggested a sudden intensification of the homograft reaction. These animals continued to excrete urine of poor quality for 8 to 12 days before anuria and eventual death resulted. In those animals in which the blood urea nitrogen remained normal, prolonged function could be expected.

The cause of death in many instances was pneumonia associated with a significant de-



a b c

FIG. 3. Normal remaining kidney of the donor of kidney transplant of dog 25. b, Control renal homograft at 7 days showing enlargement, edema, and cortical ischemia characteristic of homograft rejection. c, The renal homograft of dog 25 after 66 days in the host. There is very little enlargement or edema, but some areas of cortical hemorrhage may be seen. The transplant was still functioning at the time of the host's death.

pression of the white blood cell count and anemia. These factors were intensified by uremia in those animals in which the homograft did not continue to function.

DISCUSSION

It may be seen in Table II that the bilaterally nephrectomized dogs with a pelvic renal homotransplant but without 6-MP administration survived for an average period of 15.0 days. By contrast, the bilaterally nephrectomized dogs with a pelvic renal homotransplant who received the 5 milligrams per kilogram 6-MP regimen had an average survival time of 23.7 days. The difference between these two groups is significant, the student's T test showing a p value of less than 0.05.

The average survival of the bilaterally nephrectomized dogs (7.5 days) compares closely to the figure found by Dempster of 7.8 days. Untreated pelvic renal homografts functioned an average of 5.7 days. This figure compares very closely with the average functional survival of 5.8 days found in a large series of canine renal homotransplants when the transplant was placed in the renal fossa after removing the right kidney (5). The survival of the homografted control animals, therefore, was about what one would expect by adding together the survival period for a bilaterally nephrectomized dog plus the functional period for an untreated renal homotransplant.

The mode of action of 6-MP is that of a purine analogue, blocking the synthesis of some ribonucleic acids and thus, inhibiting the formation of proteins, presumably, including some antibodies. It appears that 6-MP is capable of effecting the rapidly dividing normal cells of the bone marrow and intestinal epithelium and those cells in the lymph node which rapidly proliferate in response to antigens of the homograft.

From the gross, microscopic, and functional studies reported in these experiments, it would appear that the prolongation of renal homotransplant function in the 6-MP treated animals was consequent upon diminution of the interstitial round cell infiltration which appears to be intimately concerned with the rejection of first set renal homotransplants. Mitchison has suggested that the major agent required for the rejection of homografts is the "immune node cell." This supposition was further strengthened by an examination of the lymph nodes of the 6-MP treated animals (Fig. 10). The microscopic appearance of these 6-MP treated lymph nodes is very similar to that seen in animals receiving 1,500 roentgens of total body radiation described previously (6). This amount of radiation to the host prevented any round cell infiltration from

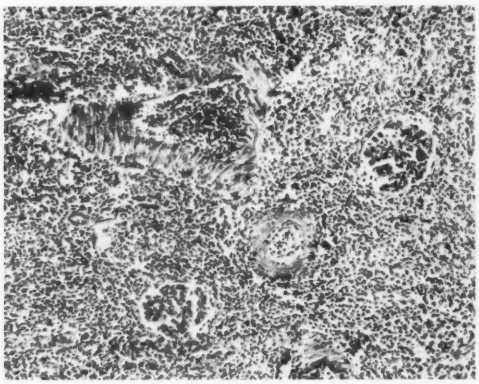


FIG. 4.

FIG. 6.

FIG. 5.

FIG. 7.

FIG. 4. Marked renal homograft reaction with lymphocytic cell infiltration and vascular thrombosis. Hematoxylin and eosin, ×60.

FIG. 5. Dog 34. A photomicrograph of the kidney transplant which functioned for 35 days. There is some tubular damage, but very little edema or round cell infiltration. Hematoxylin and eosin, ×60.

FIG. 6. Biopsy of dog 25 renal homograft on the thirtieth day. This dog lived for 66 days. Hematoxylin and eosin, ×60.

FIG. 7. The renal transplant of dog 25 after 66 days, showing extensive fibrosis and scarring and relatively little round cell proliferation. Hematoxylin and eosin, ×60.

appearing in the renal homograft and destroyed nearly all lymphoid tissue in the nodes.

The destructive action of 6-MP on lymph node germinal centers may lend support to the concepts of Ortega and Mellors, Coons, and Wissler and associates that antibody production by lymph nodes requires the presence of discrete aggregates of lymphocytes in the germinal centers. The plasma cell (once developed) is apparently capable of functioning independently and singly to produce antibodies. In these experiments, as in those dealing with total body radiation, there seems to be a rough correlation between the degree of lymph node destruction and the lack of homograft reaction.

The lymph node destruction which is apparently related to the prolonged survival of the homografts appears to lead to a greater

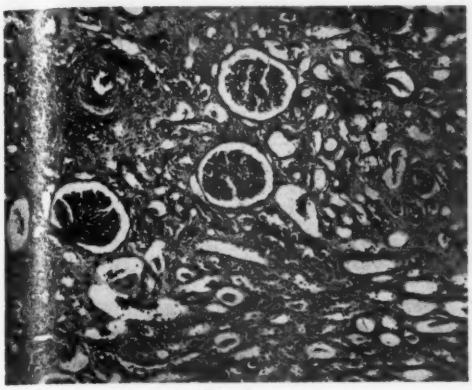


FIG. 8.

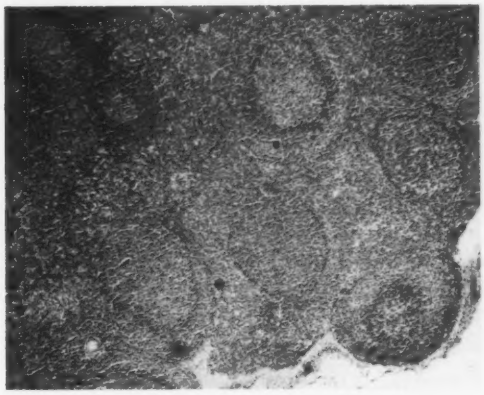
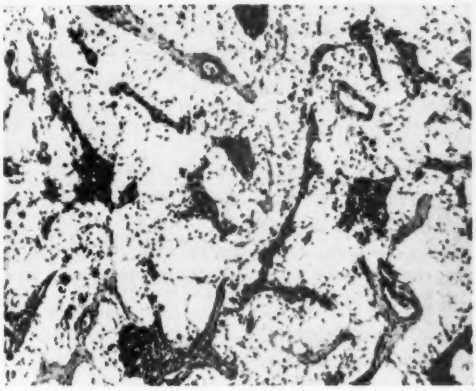


FIG. 9.



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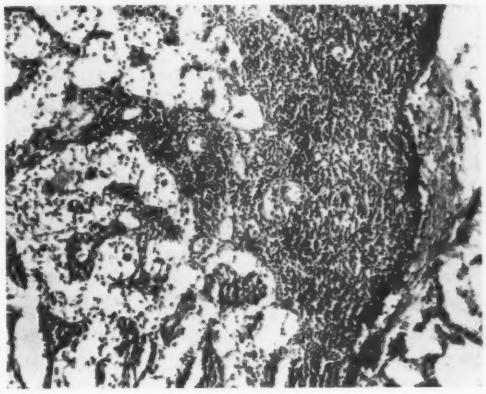

b

FIG. 10.

FIG. 8. Another cortical area of the renal transplant in dog 25 after 66 days showing tubular dilatation and some interstitial edema and tubular destruction. There is minimal round cell infiltration, and distinctly less than that seen at 30 days in a biopsy of the same kidney (Fig. 6). Hematoxylin and eosin, ×60.

FIG. 9. Normal mesenteric lymph node of a dog showing central and peripheral zones. Hematoxylin and eosin, ×24.

FIG. 10. Mesenteric lymph node of dog 34 after 35 days of 6-MP therapy, showing reduction in lymphocytes and almost complete absence of follicles. a, Central zone. b, Peripheral zone. Hematoxylin and eosin, ×60.

susceptibility to infection, since many of the animals in this series ultimately died of pneumonia. It has been pointed out by Hubay and by Meeker (8) and their associates that 6-MP appears to have the capacity to kill animals without showing any marked effect on the peripheral white blood cell count. This observation was also noted by us.

Calne has also reported prolonged survival of renal homografts in dogs treated with 6-MP. Two of his animals showed a normal microscopic appearance of the transplant after 21 and 47 days, respectively. These animals ultimately died of pneumonia.

CONCLUSIONS

1. The administration of 6-MP at the proper dose level will prolong the func-

tional survival of renal homotransplants in the dog.

2. A temporary delay in the appearance of the characteristic microscopic homograft changes can be produced by the administration of 6-MP in some instances, but a modified reaction appeared in all transplants which survived and functioned for 15 days or more. Three animals survived for 32, 42, and 66 days and still showed a normal blood urea nitrogen at the end of this period in spite of microscopic evidence of a modified homograft reaction.

3. The prolongation of 6-MP of functional renal homograft survival appears to correlate with the degree of destruction of host lymph node germinal centers.

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PREOPERATIVE RADIATION THERAPY FOR ADENOCARCINOMA OF THE RECTUM AND RECTOSIGMOID

CURTIS C. RUFF, M.D., F.A.C.S., MALCOLM B. DOCKERTY, M.D., ROBERT E. FRICKE, M.D., and JOHN M. WAUGH, M.D., F.A.C.S., Rochester, Minnesota

THE ORTHODOX TREATMENT of colorectal carcinoma is surgical, and the literature is replete with statistical analyses of the results achieved. However, to some patients the prospect of a permanent colonic stoma is unacceptable. In other instances, colorectal carcinomas may be so large and so firmly fixed that to attempt their removal surgically would impose a prohibitive mortality. In still other patients, the existence of some serious but unrelated disease process renders dangerous or inadvisable a direct and immediate surgical attack on a lesion the removal of which is technically feasible.

Under these and comparable circumstances, means other than surgical must be sought to achieve a measure of comfort for the patient. Can we hold ground while the patient comes to an understanding that there are worse fates than those imposed by colostomy? Can we reduce the size of the growth so that it may be removed? Can we banish the peril to life and limb which temporarily has rendered dangerous the performance of a Miles procedure?

Radium and roentgen therapy has found application in the preliminary handling of such problem cases of carcinoma involving the rectum and rectosigmoid, even though it is conceded that these growths are counted among the more "radioresistant" malignant lesions. Since a complete study of patients so treated has not been previously made at the Mayo Clinic, the present study was undertaken.

From the Sections of Surgery, Surgical Pathology, and Roentgenology, Mayo Clinic, and the Mayo Foundation, Rochester, Minnesota.

Abridgment of thesis submitted by Dr. Ruff to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

HISTORICAL DATA

Symonds in 1914 reported the first case of rectal adenocarcinoma treated by radium. At the time of surgical excision, 7 months later, no residual tumor was found. In the 1928 series reported by Neuman and Coryn, a number of patients with "inoperable" growths were brought into the operable category by means of preliminary treatment with radium. Four of these patients survived for 5 years. The program of Binkley (2) in 1932 consisted of preoperative therapy with roentgen rays followed by colostomy. About a week later, radium needles were placed within the growth, either from above or from below. Posterior resection followed after a 2 week interval. In those instances in which it was believed that residual tumor or involved nodes remained, postoperative therapy with roentgen rays was employed. Sixteen patients so treated were eligible for 5 year studies; 9 survived.

In a series of papers from the Mayo Clinic, Bowing and others (3–7) have presented short term results following surface and interstitial application of radium to colorectal lesions as a preliminary to surgical removal. Shedden, Gordon-Watson, Regaud, Malbin and Stenstrom, and Drueck are among others who have explored the advantages of this form of combined therapy in selected cases.

Throughout these publications, one finds little agreement as to the best time for surgical intervention following the period of irradiation. Bowing and Dixon have pointed out that surgical treatment in the early postradium period was fraught with difficulties because of a marked local inflammatory reaction featuring swelling,

TABLE I.—RADIUM TREATMENT

Method	*Cases*	*Per cent*
Singly		
Surface radiation	67	69.8
Interstitial radiation	1	1.0
Combination		
Surface radiation plus vaginal application	16	16.7
Surface radiation plus radium packs to the groin	2	2.1
Surface radiation plus interstitial radiation	5	5.2
Surface radiation plus interstitial radiation plus vaginal application	4	4.2
Interstitial radiation plus vaginal application	1	1.0

The radium therapy was supplemented by roentgen-ray therapy in 17 cases before and 7 cases after operation. The roentgen-ray therapy was delivered by either 135 or 200 kilovolt machines and consisted of external radiation to the pelvis.

edema and friability of tissues. They recommended a waiting interval of 8 to 10 weeks to allow these changes to subside. Drueck would extend this interval to 12 weeks. May, Binkley (1), and Pfahler, on the other hand, were more concerned with a resurgence of growth in those portions of the neoplasm that had escaped early destruction. Accordingly, they recommended rather prompt surgical intervention following irradiation. The "optimal" time interval would appear to depend on whether one measures the beneficial effect of irradiation on the tumor itself or on the tissue bed in which it lies. The literature is voluminous with respect to both of these important effects, but since they are to be detailed in connection with reporting the present series, they will not be reviewed at this time.

MATERIALS AND METHODS

In the period 1914 through 1943 a total of 96 patients came to the Mayo Clinic with proved colorectal carcinomas which were treated with radium and almost all of which were subsequently excised. Ancillary treatment with roentgen rays was carried out in some. All surgically excised tissues were available for study and these along with their accompanying slide collections were secured for review. New blocks of tissue were cut from the formalin-fixed original growths, from the surrounding tumor bed, and from regional nodes. These tissues were paraffin-blocked in the usual manner, and from them hematoxylin and eosin mounts were prepared. In selected instances, stains for mucus were additionally employed. Clinical records were next reviewed with special reference to the types of treatment carried out and the time relationships involved. A final clinicopathologic correlation was attempted in an effort to establish the effects attributable to irradiation.

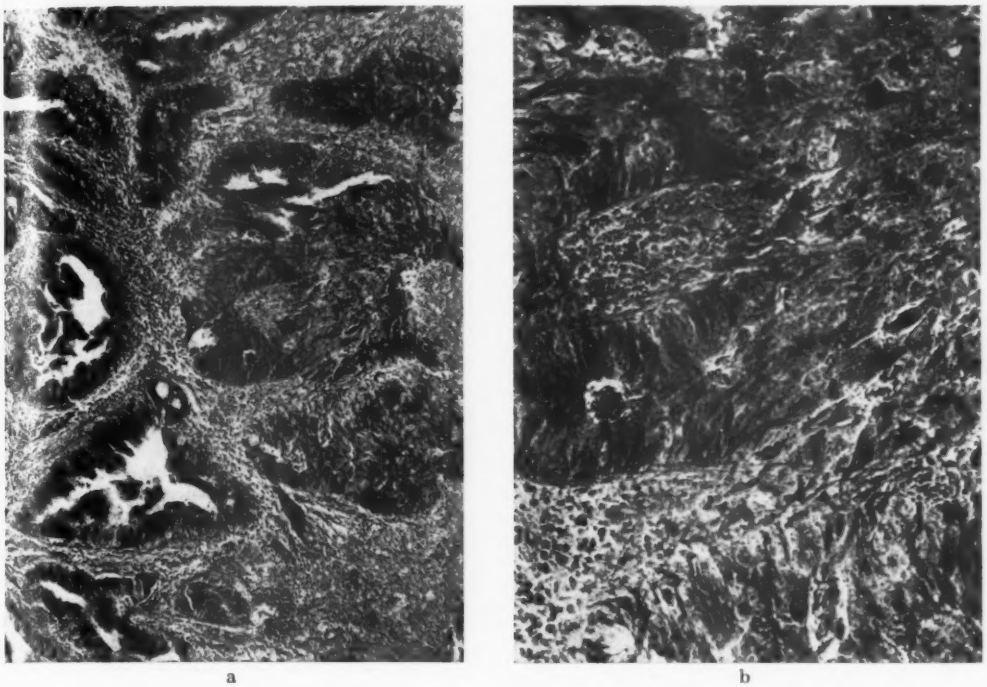
CLINICAL DATA

Sex and age. Our series comprised 63 males and 33 females. The average age at the time of diagnosis was 53.7 years, with a range from 27 to 72 years.

Local extent. Ten of the 96 lesions were clearly inoperable. This information was usually obtained by reference to the surgical dictation at the time of abdominal exploration for the purpose of establishing a colonic stoma. The remaining 86 lesions were classified as being locally removable.

Irradiation data. All patients received local irradiation either with radium element or with radon tubes, various filters being employed to remove all but the gamma rays. The dosage of radiation varied with the size of the lesion; the methods of administration are listed in Table I. Treatment was listed as being complete if, in the estimation of the therapist, all portions of the tumor received optimal amounts of irradiation. "Limited treatment" implied that portions of the growth were inaccessible or that the dose for some other reason was less than tumoricidal. Ninety-three patients received complete treatment, but in 15 of them preliminary fulguration of the lesion was necessary to facilitate the application of radium.

Considerable variation existed in the time interval between the application of radium and the surgical excision of the growth. Six weeks appeared to be a convenient dividing line, however, with 37 patients being operated upon within this span of time and 59 coming to operation beyond this period of time.



a b

FIG. 1. a, Untreated rectal adenocarcinoma, grade 2. Relatively large size of hyperchromatic nuclei gives an over-all dark staining to cells comprising malignant foci. Hematoxylin and eosin, ×65. b, Same lesion as that depicted in "a" but specimen removed 3 days after surface application of radium. Marked swelling of cells is apparent, with hydropic changes being prominent in left portion of field. Hematoxylin and eosin, ×185.

The types of surgical excision included posterior resection in 72 patients, combined abdominoperineal Miles resection in 14, and wide local excision in the remainder. In the first two categories, establishment of a permanent colonic stoma was also necessary. It should be noted that the high proportion of posterior resections reflected a type of treatment for rectal carcinoma that was in vogue during the period covered by the present study.

PATHOLOGIC FEATURES

Gross appearance. Eighty-seven of the resected segments exhibited ulcerative areas, although the ulcers present were not always malignant in appearance. Six showed polypoid and 2 papillary lesions. In 1 instance the bowel mucosa was intact, and no evidence whatsoever suggesting the presence of a malignant process could be found. As compared with lesions from an unselected control series, the following differences are worth emphasizing: The extent of necrosis was more pronounced than in growths not treated by radium. This fact was most noticeable in the "short-interval" category. In about 60 per cent of cases, the growths, the adjacent bowel mucosa, and the underlying tumor bed were noticeably edematous. Again, patients operated upon soon after therapy with radium exhibited the most pronounced degrees of edema in and about the carcinoma. Unusual degrees of perirectal fibrosis furnished an additional feature of interest. Rarely observed in lesions from the "short interval" category of patients, no less than 63 per cent of those in the

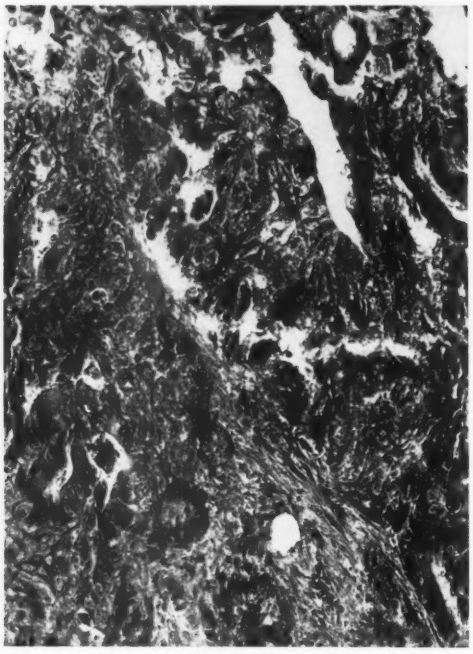


FIG. 2.

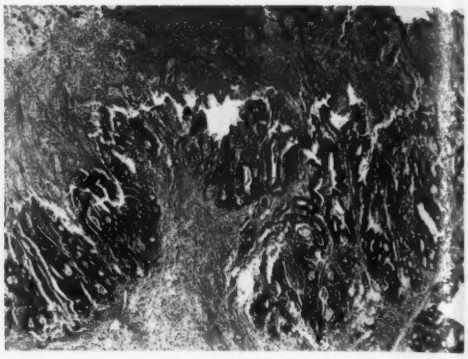


FIG. 3.

FIG. 2. Severe irradiation change. Many of the tumor cells are indistinct in outline, and some are swollen with hydropic change. Some nuclei are identifiable but pyknotic; identity of others is lost in dense chromatin masses. Inflammatory infiltrate is present. Hematoxylin and eosin, ×135.

FIG. 3. Obviously necrotic tissue and just as obviously viable tissue are here intermingled from a lesion in which there was a long delay between irradiation therapy and surgical removal. Hematoxylin and eosin, ×21.4.

"delayed" category manifested this fibrotic change.

Regional nodes were small anddifficult to find, except in cases in which they were involved by metastatic carcinoma.

Microscopic features. Tumor and nodal changes.—It was soon apparent in our study that the degree of cellular damage sustained by the tumor was not uniform. Areas of severe destruction could be seen alongside zones of actively dividing tumor cells in the same microscopic field. The following changes, interpreted as representing irradiation effect, could be noted as early as 3 days after radium application: Marked cellular swelling, both nuclear and cytoplasmic, was first observed (Fig. 1a and b). Nuclear chromatin began to clump; the nuclear membrane became irregular in outline. The cytoplasm took on a granular or muddy appearance and then proceeded to vacuolate. Following this the cells either fragmented completely or shrank in size, with nuclear material aggregating into pyknotic clumps which stained intensely with hematoxylin (Fig. 2). Cell fusion sometimes occurred with loss of individual cell outlines. Other cells, losing completely their affinity for stains, could aptly be described as ghost cells. Zones rich in ghost cells were often the seat of complete necrosis.

An attempt was made to appraise the tumoricidal effects of irradiation through ranges of mild, moderate, severe, and complete. In 16 cases, there appeared to be little or no actual destruction of tumor tissue. In 43 cases, somewhat more viable than nonviable tissue was evident (Fig. 3). In 27 cases, more than half of the neoplastic cells appeared to have been destroyed. Finally, in 10 instances, no residual malignant tissue could be found upon examination of the specimen. Nine of the 10 patients harboring these "disappearing" growths had had their definitive operation 6 weeks or longer after therapy and irradiation. Yet, paradoxically enough, pronounced but short

of complete destruction of the neoplasms was observed in a much higher proportion of patients in the "short interval" category.

The tumoricidal effects of irradiation on metastatically involved nodes was not so apparent as it was on the primary growths. Malignant nodal involvement occurred in 38 per cent of cases. This figure is low compared to that expected in a control series, and we offer it as our only positive evidence that radium sterilized these structures once they became seeded with malignant cells.

The tumor bed.—Microscopic evidences of edema, inflammatory infiltration, fibrosis, and hyalinization characterized the changes in the tumor bed. Some of these have been referred to in the section dealing with gross findings. It was apparent from a sequential study of events that collagenous material eventually became deposited in zones which earlier had been the seat of edema (Fig. 4). An inflammatory reaction consisting of lymphocytes, plasma cells, and polymorphonuclear leukocytes was found principally around lesions from the "short term" category (Fig. 5). These inflammatory elements tended to occur in proximity to zones of necrosis on the deeper aspects of the tumor and to areas of edema in the tumor bed (Fig. 6). This infiltrate tended to subside with the passage of time, and it was never observed, in severe degree, in connection with lesions from the "long term" category.

The blood vessels.—Vascular changes in the tumor bed had not been observed grossly, but microscopically they comprised one of the most interesting effects of irradiaiton. Edema of blood vessel walls was the earliest alteration noted. It was followed in a matter of days by intimal and subintimal proliferations of endothelial cells and fibroblasts respectively (Fig. 7). As a consequence, even small vessels became greatly thickened and their lumens narrowed. Thrombosis was a frequent sequel along with fibrosis. These changes—with a terminal tendency to fibrous thickening—

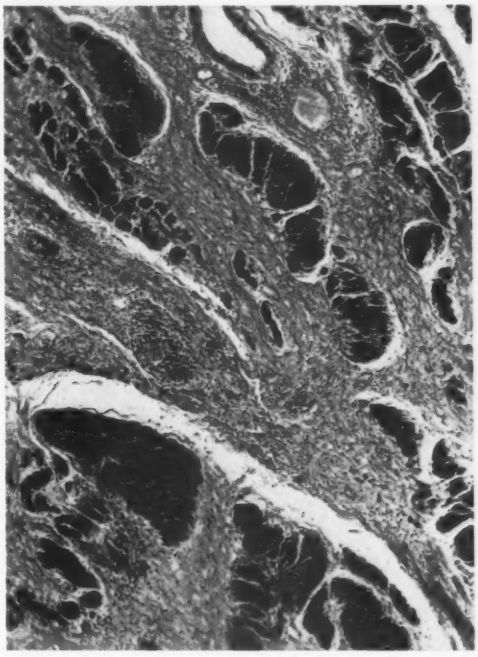


FIG. 4. Interstitial fibrosis of muscle, as of other tissue, occurs as a late manifestation of irradiation response. It usually occurs in areas that were earlier the site of edema. Hematoxylin and eosin, ×60.

appeared to progress with the passage of time (Fig. 8). They were found in all coats of the bowel wall and even in the perirectal and pericolonic tissues.

The nerves.—Cells of the myenteric plexus appeared to be unaltered. It was not unusual to discover clusters of seemingly intact ganglion cells in a zone in which all neighboring elements were in a state of disintegration.

The surrounding mucosa.—This tissue exhibited swelling and edema of elements in the lamina propria along with hydropic degeneration and focal destruction of the epithelial elements.

END RESULTS OF TREATMENT

After deleting from analysis the 9 hospital deaths, 87 patients remained for follow-up studies. Of these, 38, or 43.7 per cent, survived 5 years after excision of their lesions.

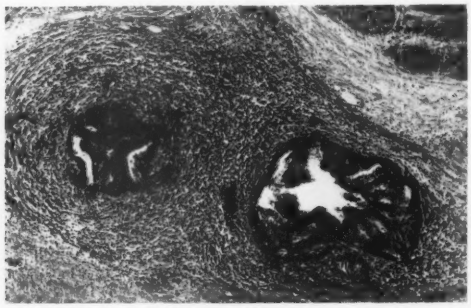


FIG. 5.

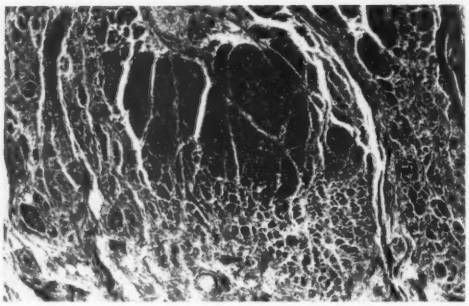


FIG. 6.

FIG. 7.

FIG. 5. Marked lymphocytic and plasma cell infiltrate is herein depicted as an example of early reaction within tumor bed. Hematoxylin and eosin, ×48.

FIG. 6. Marked edema of muscle bundles in tumor bed is here portrayed. Hematoxylin and eosin, ×37.

FIG. 7. Early changes in the blood vessels feature edema and endothelial proliferation with consequent narrowing of the lumens. Hematoxylin and eosin, ×45.

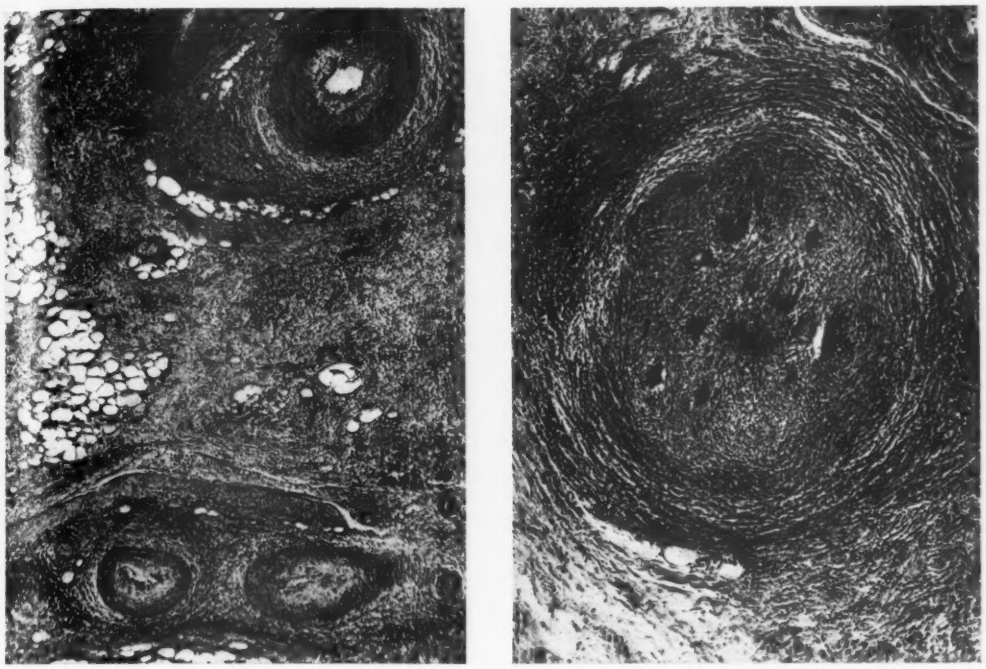
Breakdown according to type of operation revealed 5 year survival rates of 66.7 per cent, 41.5 per cent, and 30.0 per cent for combined abdominoperineal resection, posterior resection, and wide local excision respectively. By present-day standards, these last two procedures would be considered somewhat short of ideal.

Early operation yielded poorer results—5 year survival rate of 37.5 per cent—than did those that were delayed beyond the 6 week period—47.3 per cent. Certain reasons for this difference are detailed under "Comment."

Twenty-eight of 54 patients, 51.9 per cent, with uninvolved nodes survived for more than 5 years, whereas only 10 of 33 with nodal secondaries were so fortunate. With respect to tumor grading, 13 of 16 patients with Broders grade 1 lesions survived 5 years, whereas none of the 5 individuals with grade 4 growths survived for appreciable periods postoperatively. Corresponding figures for grade 2 and grade 3 lesions were 38.0 per cent and 37.5 per cent respectively.

Of interest was the fact that the 5 year survival group included 4 of 10 patients whose originally inoperable lesions had been made surgically removable by means of preoperative radium therapy.

The fate of 10 patients whose lesions were apparently completely eradicated by radium treatment, sometimes preceded by local fulguration, was as follows: There was 1 operative death. Another patient succumbed within 2 years from the effects of an independent squamous cell carcinoma



a b

FIG. 8. a, Vascular and perivascular fibrosis with thrombosis and organization occur as late phenomena in irradiated tissues. b, Granulation tissue within lumen of perirectal arteriole contains giant cells.

of the lung. The postoperative duration of life for the remaining 8 was 19, 17, 15, 12, 11, 11, 5, and 4 years respectively.

COMMENT

Tumor cell changes induced by irradiation and so well described by Ewing and by Warren were all observed in this study. Hydropic degeneration and vacuolization of cytoplasm along with nuclear swelling, pyknosis, and karyorrhexis were consistently found. Likewise apparent were certain stromal alterations like edema, and inflammatory cell infiltrations followed by fibrosis and hyalinization. Clearly and early apparent were occlusive changes involving blood vessels. Nerve cells alone appeared to escape visible alterations. Evidence from our study confirmed the fact that the microscopic changes induced by irradiation could occur as soon as 3 days after the start of treatment by this method.

Since, in our series, the interval between irradiation and surgical excision varied within wide limits, an attempt was made to plot the changes noted with respect to time. It was found that stromal and tumor edema along with the inflammatory cell response occurred during the early phases of the irradiation reaction, whereas fibrosis and hyalinization were late phenomena. In a similar sequence, edema and subintimal proliferation in blood vessels preceded fibrosis and thrombosis of these structures.

Our study demonstrated that the local lesions of colorectal adenocarcinoma could, at times, be completely eradicated by the judicious application of radium alone. In 10 of our cases, this surprising effect was achieved, there being no evidence of re-

sidual carcinoma found in the surgically excised tissue. Evidence for a similar "sterilizing" effect on involved lymph nodes was not clearly confirmed.

That an occasional malignant lesion may be rendered operable through shrinking with radium therapy was one of the positive findings in our series. In no less than 10 of our patients, the lesions were thus reduced to "surgical size" by this method, and 4 of these patients were alive at the end of a 5 year period of study.

It was considered impossible to determine, from our data, the optimal time for surgical intervention following therapy with radium. On the surface there appeared to be a 10 per cent better result for patients in the "long interval" category. However, analysis revealed that a disproportionately high number of these patients harbored low grade lesions with a reduced incidence of nodal metastasis. A second feature introducing bias into the comparative analysis was the observation that all of the combined abdominoperineal resections had been performed on patients in this "long interval" category. However, since many of the lesions studied in both groups of patients contained masses of actively growing carcinoma cells, it would seem unwise to permit an unduly long interval to elapse prior to the time of surgical removal.

Finally, we were unable to answer the question as to whether the over-all survival rate for patients with colorectal carcinoma could be improved by the routine employment of radium as a preoperative measure. Our 5 year survival rate of 43.7 per cent compares favorably with that obtaining from the orthodox surgical management over the same period. Our series was highly selected and, whereas certain lesions were originally inoperable, others would have been considered ideal for primary excision had the attitude or the general condition of the patients permitted this approach. Under these circumstances it is fair only to claim that in our series of 96 patients, the preoperative application of radium to their colorectal carcinomas proved to be a well advised decision.

SUMMARY AND CONCLUSIONS

A study has been presented of 96 patients whose adenocarcinomas of the rectum and rectosigmoid were treated with radium prior to their removal by surgical means.

Within the tumor, radionecrosis was preceded by swelling, hydropic change, and vacuolization of cell cytoplasm. Nuclei, early swollen and hyperchromatic, later became shrunken, pyknotic, and karyorrhectic. The necrotizing effect was not uniform, since necrotic and actively growing tumor tissue could sometimes be seen side by side in the same microscopic section.

Early edema and inflammatory infiltration of the tumor bed gave place later to fibrosis and hyalinization. Sequential blood vessel changes included endothelial proliferation and edema followed by fibrous thickening, thrombosis, and organization.

Radium can, at times, completely destroy an adenocarcinoma of the rectum. In 10 of our cases, no residual carcinoma was found in the operative specimen. Radium sometimes makes an inoperable lesion operable. We observed 10 such instances, in 4 of which a 5 year survival was achieved.

The over-all 5 year survival rate was 43.7 per cent with the best results, 66.7 per cent, obtaining in patients who had Miles procedures.

The optimal time for surgical attack on the tumor after irradiation was not determined in this study.

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ANURIA OF HYPOVOLEMIC SHOCK RELIEVED BY TRIS (HYDROXYMETHYL) AMINOMETHANE (THAM)

ROBERT H. GOETZ, M.D., CARLOS A. SELMONOSKY, M.D., and
DAVID STATE, M.D., F.A.C.S., New York, New York

IT IS GENERALLY HELD that the anuria accompanying hemorrhagic shock is the result of a disproportionate diminution in renal blood flow caused by renal vasoconstriction. Experiments carried out by Corcoran and Block and their associates on denervated kidneys and during direct stimulation of the renal nerves suggest that vasoconstriction once established is mediated by a humoral factor.

Glomerular filtration is known to cease when the mean blood pressure reaches levels below 60 millimeters of mercury, but anuria may be observed during hypovolemic states when the blood pressure is as high as 100 millimeters of mercury. Hemorrhagic shock is associated with metabolic acidosis and the lowest renal blood flows were observed with the lowest *p*H by Lauson and coworkers. Existing evidence points to the fact that the anuria is intimately linked with the *p*H and may be relieved by alkalizing agents.

With the availability of a new amine buffer tris (hydroxymethyl) aminomethane (THAM) which is a reversible hydrogen ion acceptor forming compounds with carbonic and other acids and which affects both extracellular and intracellular *p*H the problem of anuria in hemorrhagic shock seemed well worth investigating anew.

METHODS

The experiments were carried out on 12 mongrel dogs weighing 15 to 30 kilograms. The dogs were anesthetized with 35 milligrams of pentobarbitol per kilogram of weight and intubated. The saphenous artery and vein of one leg were used for recording arterial and central venous pressure; the femoral artery of the other side was used for bleeding. All dogs received 3 milligrams of heparin per kilogram intravenously.

A small suprapubic incision was made and the ureters were cannulated just above the bladder. The urinary flow was recorded by a drop recorder previously described (4), and a calibrated reservoir. All solutions were administered at a constant rate via the external jugular vein and the rate recorded by a second drop recorder. Arterial and urinary *p*H was determined at intervals at room temperature with a Beckman G *p*H meter.

For the bleeding, the femoral artery was connected to a reservoir kept at a height which would produce the desired blood pressure. Adjustments in blood pressure were made by adjusting the height of the reservoir. Mean blood pressure was maintained between 40 and 50 millimeters of mercury during the period of bleeding. The blood was retransfused before shock had become irreversible.

Although each dog served as its own control, developing anuria on bleeding before THAM was administered, 3 dogs were bled only and THAM was withheld to establish a baseline for the study. Three dogs received normal saline, 0.6 molar sodium chloride, or 4.5 per cent urea in normal saline prior to and during bleeding. Nine animals received a 0.6 molar solution of THAM, either prior to, during, or after bleeding.[1]

From the Department of Surgery, Albert Einstein College of Medicine, New York. Supported by Grants H-4248 and H-3743 from the National Institute of Health.

[1]One liter of a 0.6 molar solution of THAM contains: 72.6 grams of THAM, 71.5 milliequivalents of chloride, 62 milliequivalents of sodium, and 9 milliequivalents of potassium.

RESULTS

Controls. In all animals urinary flow diminished with the onset of bleeding. Complete anuria developed usually within 2 minutes (Fig. 1). In some instances, anuria was established while bleeding was still in progress, and before the ultimate fall in blood pressure to 40 millimeters of mercury was recorded. In none of the dogs did the urinary flow resume before any of the shed blood was retransfused. With retransfusion urinary flow started, as a rule, when about 30 per cent of the shed blood had been administered. Hypovolemia and its accompanying anuria were maintained for a minimum of 60 minutes. Diuresis developed after all the blood was retransfused. In all experiments the mean blood pressure during the period of bleeding was kept between 40 and 50 millimeters of mercury and the average maximum amount of bleeding was 48 cubic centimeters per kilogram—46 to 51 cubic centimeters per kilogram. The arterial *p*H fell gradually in all cases and in many animals reached levels below 7.20 during the first hour of bleeding.

The effect of administration of fluids prior to and during bleeding. The intravenous administration of normal saline at a rate of 6 cubic centimeters per minute prior to bleeding produced marked diuresis, the urinary flow increasing on the average from 0.40 to 1.70 cubic centimeters per minute. However, on bleeding, urinary output stopped abruptly despite the continued administration of saline at the same rate. Urinary flow resumed only when the shed blood was retransfused.

Similarly, the intravenous administration of a 0.6 molar solution of sodium chloride at the rate of 8.5 cubic centimeters per minute prior to and during bleeding did not prevent anuria (Fig. 2).

When a 4.5 per cent solution of urea in normal saline was administered at the rate of 4 cubic centimeters per minute prior to bleeding, urinary flow increased from 0.16 to 3.00 cubic centimeters per minute. Anuria developed instantly as the animal was bled

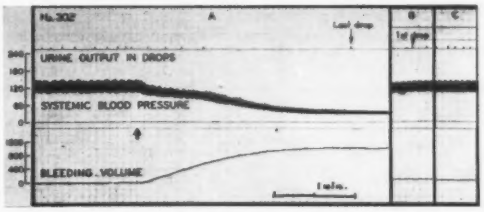

FIG. 1. Urinary output (in drops), systemic blood pressure and bleeding volume simultaneously recorded in a control experiment during bleeding (*A*), 15 minutes after onset of anuria (*B*), and 5 minutes later (*C*). Note anuria developing before blood pressure reaches the preset level of between 40 and 50 millimeters of mercury. Return of blood pressure and resumption of urinary flow in *B* after retransfusion of the blood. Slight increase in urinary output in *C*.

despite the continued administration of urea at the same rate. The total amount of a 4.5 per cent solution of urea administered in Figure 3 was 520 cubic centimeters.

The effect of THAM administered prior to and during bleeding on urinary flow. When a 0.6 molar solution of tris (hydroxymethyl) aminomethane (THAM) was administered prior to bleeding at the rate of 2.4 to 5.0 cubic centimeters per minute a profuse diuresis was obtained (Fig. 4). If its administration was continued during bleeding, there occurred a temporary diminution in urinary output only but anuria never developed. In fact, urinary output increased and a virtual diuresis developed with the continued administration of THAM despite the hypovolemic hypotension (Fig. 4).

However, if anuria had been allowed to develop with bleeding, administration of THAM was able to restore urinary flow (Fig. 3). Once a urinary output had been established under these circumstances by the administration of the buffer, any decrease in the amount administered was immediately reflected in a decreased rate of flow and anuria recurred if the administration of THAM was discontinued while the hypovolemic state persisted. The average amount of bleeding was 62 cubic centimeters per kilogram—48 to 77 cubic centimeters per kilogram. The urinary flow in dogs receiving THAM during hemorrhagic hypotension averaged 1.70 cubic centimeters

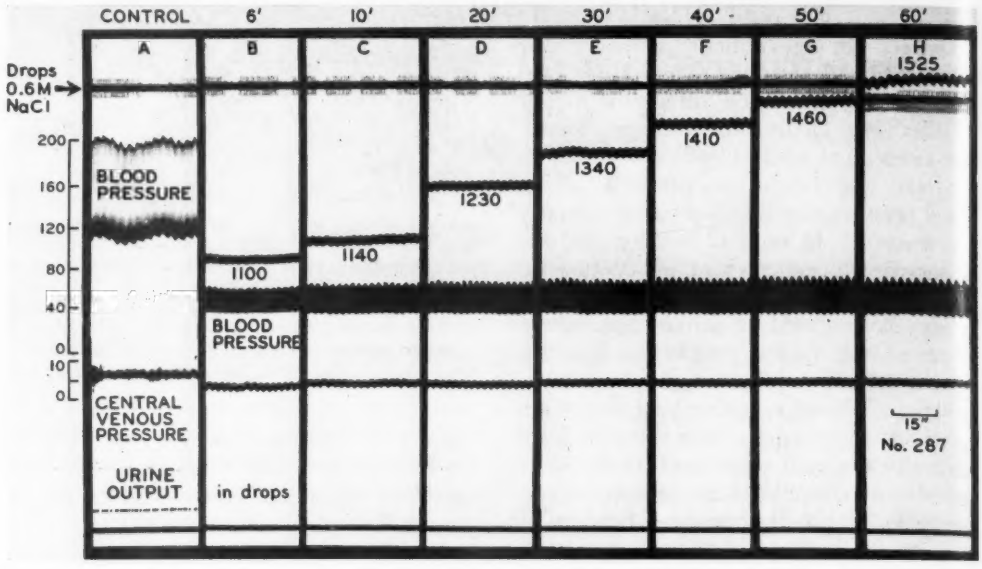

FIG. 2. Cuttings of the original tracing taken during 60 minutes of bleeding while 0.6 molar solution of sodium chloride was administered at constant rate (uppermost drop recording). Blood pressure, central venous pressure, amount of bleeding in cubic centimeters, and urinary output all simultaneously recorded. *A*, Control values before bleeding. Lowermost recording equals drop recording or urinary output. Note diuresis. *B*, Six minutes after onset of bleeding, 1,100 cubic centimeters of blood having been withdrawn. *C* to *H*, Cuttings at times indicated. Note persistence of anuria despite continued administration of saline during hemorrhagic shock. Maximal amount of bleeding—1,525 cubic centimeters equal to 75 cubic centimeters per kilogram—reached at *H*, i.e., 1 hour after onset of bleeding. Arterial *p*H at *A*, 7.49; at *C*, 7.39; at *E*, 7.28; and at *H*, 7.23.

per minute 0.6 to 2.7 cubic centimeters per minute—which is well above the control levels before bleeding in the untreated dog.

The drop in the arterial *p*H normally observed with bleeding was easily prevented by the administration of THAM and the *p*H in our experiments ranged between 7.60 and 7.78 during the hemorrhagic shock depending again on the rate of administration. Although it was our aim to administer THAM at a rate which would keep the arterial *p*H at a level of 7.6, this was difficult to achieve. The discontinuation of the buffer during hemorrhagic shock produced only a gradual decrease in arterial *p*H. Urinary flow decreased rapidly and out of proportion to the fall in *p*H and in some dogs the arterial *p*H actually remained well above 7.50 after THAM had been discontinued yet anuria developed (Fig. 3).

The urine produced by these dogs during hemorrhagic hypotension and the administration of the buffer was alkaline with a *p*H near 8.00. The exact amount of buffer which has to be administered in order to produce urinary flow and the relation between the arterial *p*H and urinary flow during hypovolemic states has still to be determined.

DISCUSSION

The acidosis accompanying hypovolemic states and its effects on renal function have been studied by numerous investigators. Lauson and associates found that the lowest clearances were associated with the lowest *p*H but did not think that acidosis was the cause of the diminished urinary flow because some of their patients regained renal function after blood volume replacement

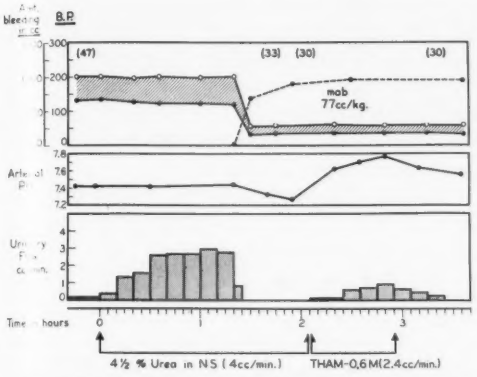

FIG. 3. Chart shows effect of 4.5 per cent urea and of a 0.6 molar solution of THAM on urinary output during bleeding. Note diuresis before and anuria after bleeding despite continued administration of urea. Resumption of urinary flow with administration of THAM and decrease in urinary flow and anuria after discontinuation of buffer. Figures in parentheses indicate hematocrit. Maximum amount of bleeding: 77 cubic centimeters per kilogram.

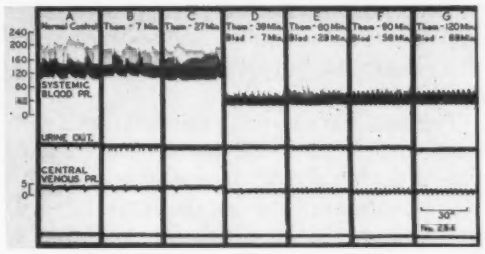

FIG. 4. Prevention of anuria normally accompanying bleeding by the administration of THAM. Cuttings from original tracing taken at indicated time intervals. *A*, *B*, and *C* obtained before bleeding, *A* before the administration of THAM, *B* and *C*, 7 and 27 minutes, respectively, after administration of THAM. Note the development of marked diuresis. *D* and *G* obtained during bleeding, THAM being administered at same rate as in *B* and in *C*. Note the temporary decrease in urinary output but no anuria in *D* and the development of marked diuresis in *G* while the animal is still in hemorrhagic shock—maximum amount of bleeding 52 cubic centimeters per kilogram. Arterial *p*H in *A*, 7.50; *B*, 7.56; *C*, 7.64; and in *D* to *G*, 7.75.

despite maintaining a low arterial *p*H. In the isolated kidney urinary flow depends largely on the *p*H of the perfusate, the highest urinary flows being recorded with the higher *p*H. Our experiments demonstrate that THAM, an organic amine buffer, is not only effective in preventing or reversing the anuria associated with hypotension caused by large hemorrhage, but is able to induce marked diuresis at blood pressure levels which normally are associated with a non-secreting kidney. Whether this is brought about by the effect of elevating the arterial *p*H on the function of the nephronic cell or indirectly by decreasing the renal vascular resistance or whether we are dealing with a solute load diuresis cannot be said at this point. However, observations by Nahas, Jordan, and Ligou confirm that THAM is eliminated in its ionized form with an equimolar amount of bicarbonate, thus acting at least partially as an osmotic diuretic.

There is no difficulty in preventing or correcting the acidosis accompanying hemorrhagic shock by the administration of THAM, an organic amine buffer which is able to draw large amounts of carbon dioxide from the saturated tissues into the blood stream. As the acidosis accompanying hemorrhagic shock is not due to the loss of base but explained by the accumulation of acid cellular products and an increase in carbon dioxide in the body stores in the presence of a functionless kidney, the prevention of anuria or the development of diuresis during hemorrhagic shock may prove important as it will allow the kidney to make the necessary adjustments by appropriate selective excretion of acid radicles.

Similarly, the anuria produced by apneic oxygenation can be abolished by the administration of THAM. The studies of Nahas suggest that in progressive hypercapnic acidosis the $H+$ concentration may have a direct effect on the excretory and secretory functions of the nephron. Diuresis has been observed after bicarbonate infusion in cases of renal failure. However Burnett and associates found that this did not necessarily have a beneficial effect on the kidney.

There may be a difference, however, between the correction of *p*H with bicarbonate and THAM. Robin was able to demonstrate that the former has little effect on the intracellular *p*H whereas THAM was able to

penetrate the cell, resulting in approximately equivalent intracellular and extracellular *p*H changes on intravenous administration of THAM.

The fact that anuria developed rapidly in our experiments if the buffer was discontinued during shock, despite a persistently high *p*H would suggest that the actual arterial *p*H itself is not the sole determinant of urinary flow. This is in agreement with observations of Thompson and Barrett who gave bicarbonate to dogs in whom they had decreased the glomerular filtration rate by partial aortic obstruction. The arterial *p*H remained high after bicarbonate administration had been discontinued but urinary output dropped.

SUMMARY

The anuria and acidosis associated with hemorrhagic shock have been investigated. They could not be prevented by the administration of normal saline, 0.6 molar sodium chloride, or 4.5 per cent solution of urea.

THAM, a new amine buffer, prevents both the acidosis and anuria of hemorrhagic shock if administered prior to and during bleeding.

Once established, anuria can be relieved by the administration of THAM, and in fact, diuresis develops despite the continued hypovolemic hypotension, i.e., blood pressure levels between 40 and 50 millimeters of mercury and bleeding of 48 to 77 cubic centimeters per kilogram.

The possible mechanisms by which THAM relieves the anuria associated with hemorrhagic shock are discussed.

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ROENTGENOGRAPHIC AND SURGICAL ASPECTS OF VASCULAR ANOMALIES OF THE SPINAL CORD

HENDRIK J. SVIEN, M.D., F.A.C.S., and HILLIER L. BAKER, JR., M.D.,

Rochester, Minnesota

THE CLINICAL and pathologic aspects of vascular anomalies of the spinal cord have been well presented and reviewed by a number of authors, among them Wyburn-Mason; Brion, Netsky, and Zimmerman; Brasch; Suter-Lochmatter; and more recently, Newman (9, 10). Inasmuch as our survey of these aspects adds little to what already has been written, we shall confine our discussion to the roentgenographic and surgical aspects of these lesions.

From all the cases on record at the Mayo Clinic we have culled 32 cases in which sufficient documentation was available for proper study. Undoubtedly, many valid cases were rejected. Our study has been confined to primary intradural vascular anomalies of the spinal cord which were subdivided into the following categories: venous anomalies, 15 cases; arteriovenous anomalies, 15 cases; telangiectasis, 2 cases.

ROENTGENOLOGIC ASPECTS

Such lesions frequently cause alterations in the dynamics of the cerebrospinal fluid and its total protein and cellular content, but measurement of these abnormalities may not suggest the proper diagnosis. Roentgenographic examinations are the only diagnostic procedures by which the character and extent of a lesion may be determined accurately prior to its exposure at operation.

Positive contrast myelography. Routine roentgenograms of the spine yielded little helpful diagnostic information in this series. Among 22 cases in which positive contrast myelography was used, however, we were able to make an accurate diagnosis in 19, based on observation of the characteristic appearance described first by Guillain and Alajouanine and subsequently by Lombardi and Migliavacca and others. In 2 other cases myelographic abnormalities were observed but were not considered diagnostic, and in only 1 were the findings from this examination considered completely normal. This experience varies greatly from that of Brion and associates, who found the myelogram was "rarely diagnostic."

In any case that affords clinical evidence of involvement of the spinal cord itself, we prefer to install 9 to 12 milliliters of ethyl iodophenylundecylate (pantopaque) in the lumbar spinal subarachnoid space. This medium then is caused to move up and down the spinal canal, under constant roentgenoscopic observation, with the patient in the prone position. When suspecting the presence of a vascular anomaly, it has been found useful to employ the oblique and supine positions as well, in order to outline it more completely. Spot films are made in the course of the examination to record the observed abnormalities.

Characteristically the vessels that comprised the vascular anomaly were visualized as negative shadows in the contrast medium. These vessels varied from 1 to 4 millimeters in width and were unmistakably distinguishable from the normal spinal arteries by their greater number and their erratic, tortuous configurations (Figs. 1 to 3). In some cases the abnormal vessels were shown to involve the entire length of the spinal canal (Fig. 4a), whereas in others

From the Sections of Neurologic Surgery and Roentgenology, Mayo Clinic, and the Mayo Foundation, Rochester, Minnesota.

a FIG. 1. b

a FIG. 2. b

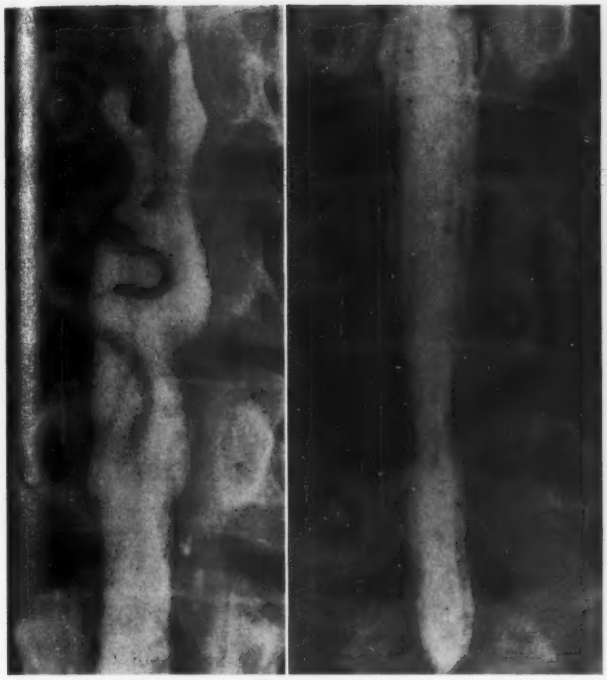
FIG. 1. a and b, Arteriovenous anomaly involving the conus and cauda equina. Multiple tortuous vessels of large size, 4 to 5 millimeters, well demonstrated.

FIG. 2. a and b, Vascular anomaly of the entire spinal cord below the first thoracic vertebra. The vessels were only 3 millimeters in diameter at the most, but their multiplicity caused partial obstruction of the subarachnoid space.

a more localized involvement was seen (Fig. 4b). The subarachnoid space was encroached upon to an extent depending upon the size of these vessels, and consequently a complete block to the flow of pantopaque was observed in 3 cases (Fig. 5a) and a partial block in 11. It was apparent that expansive involvement of the spinal cord itself was partly responsible for the obstruction in several cases (Fig. 5b). When obstruction was complete, the cephalad margin of the pantopaque assumed an irregular serrated appearance and enlarged tortuous vessels were visible extending at least 2 or 3 segments caudally. Vigorous pulsation of the abnormal vessels in 3 cases enabled us to recognize the arteriovenous character of the anomaly at the time of myelography. If no pulsation was observed, it was impossible to differentiate between the purely venous and the arteriovenous malformations.

The main conditions which must be distinguished myelographically from vascular anomalies are adhesive arachnoiditis and, in the presence of complete block, spinal cord tumors. In arachnoiditis the opaque medium assumes an irregular, patternless configuration with no evidence of the presence of serpiginous vascular structures—an appearance which rarely, if ever, resembles that of vascular lesions. Spinal cord tumors, even those with demonstrable contiguous vascular engorgement, cause such characteristic myelographic deformities that their diagnosis should not be difficult. It should be remembered that enlarged vessels associated with a tumor are seen only in the immediate vicinity of that lesion (Fig. 6), whereas those of a primary vascular malformation extend over many segments of the spinal canal (Fig. 5a).

Other roentgenologic methods. Although myelography is, at the present, the only roentgenographic method which consistently demonstrates these vascular lesions, Hook



a FIG. 3. b

a FIG. 4. b

FIG. 3. a and b, Vascular anomaly of entire spinal cord and cauda equina. Note the large vessels in the region of the conus medullaris but only tiny vascular channels below.

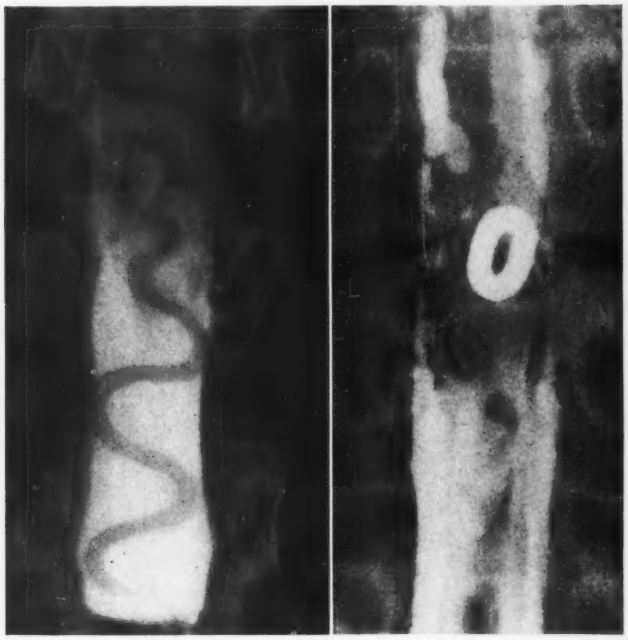
FIG. 4. a, Unusual myelogram demonstrating abnormal vessels along the entire length of the spinal cord. The patient was supine, and 9 milliliters of pantopaque were used. b, Localized arteriovenous anomaly confined to the segments between the seventh cervical and fourth thoracic vertebrae. Note the deviation of the spinal cord to the left and the normal anterior spinal artery shadow below.

and Lidvall recently reported 2 cases in which upper cervical lesions were visualized angiographically. Using their technique, we were unable to demonstrate abnormal vessels by vertebral angiography in 2 of our patients who had cervical lesions.

In 4 patients with myelographically proved involvement in the dorsal region, transosseous venography was performed with the hope that a more graphic depiction of the extent and severity of the changes might be obtained. Disappointingly, so many venous channels were opacified that it was impossible to distinguish the abnormal from the normal vessels (Fig. 7a and b), and, consequently, this method of examination has not proved helpful.

At the present time, the feasibility of demonstrating the arteries of the spinal cord by means of aortography is being investigated. Thus far our studies have been confined to cases of aortic occlusive disease. The results have been somewhat encouraging, but it remains to be seen whether this technique will be of value in the diagnosis of vascular anomalies of the spinal cord and other neurologic lesions.

Another newer roentgenologic technique that we are beginning to utilize in myelography is cineradiography. In vascular anomalies it may be possible to record pulsations of the vessels not ordinarily visible by fluoroscopy and thus to establish the arteriovenous character of the lesion in a greater number of cases. Such records



a FIG. 5. b

FIG. 5. a, Complete obstruction of the subarachnoid space due to an extensive vascular anomaly of the spinal cord. The area of obstruction is quite irregular in its outline. Enlarged vascular channels extend many segments below the site of the block. b, Partial obstruction of the subarachnoid space due to localized vascular anomaly expanding the spinal cord. Such expansion could be due either to hemorrhage or to the bulk of the vessels.

FIG. 6. Complete subarachnoid obstruction caused by an intramedullary glioma. Vascular engorgement is seen only in the immediate vicinity of the tumor.

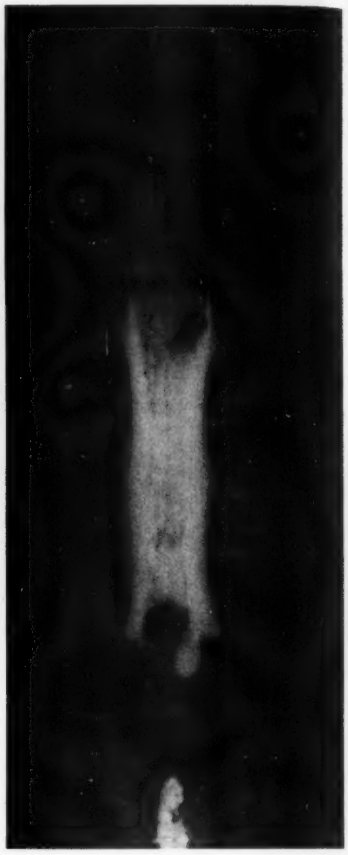


FIG. 6.

will be of great value also in the teaching of myelographic technique.

SURGICAL ASPECTS

Reports of others. Wyburn-Mason surveyed the results of surgical treatment reported up to 1943. The experience in venous anomalies was summarized as follows:

In 25 cases laminectomy alone has been performed with closure of the dura. Three cases died after operation, 4 became worse, 11 were unchanged and 5 showed very slight improvement. In 6 cases the dura was left open to try and decompress the cord. One died of wound infection, 3 were unchanged and 2 showed slight improvement. In 19 cases attempts to ligate and remove some or all of the dorsal pial veins has been tried. In 7 cases death followed, in 5 cases the patient was either worse or practically unchanged, and in 7 cases . . . there was remarkable improvement. Ritter electro-coagulated the veins with disastrous results, the patient dying shortly after operation. Post-mortem examination of patients, who have died after attempts at excision or electro-coagulation, reveal extensive fresh thromboses in the intramedullary veins with fresh degeneration of ascending tracts. Puusepp claimed cure in 2 cases by cutting the posterior roots.

For Wyburn-Mason's review of arteriovenous anomalies treated surgically prior to 1944, only a few reports were available. In 1 case removal of some of the vessels was attempted, but no improvement followed. In another instance the nutrient vessel was ligated without benefit.

To his survey of published accounts, Wyburn-Mason appended several groups of new reports. These included 13 cases of venous anomaly in which operation was carried out. Laminectomy and decompression were performed in 12, after which the patients' condition was worse in 3 and unchanged in 9. In the thirteenth case the veins were ligated also, and that patient was worse after operation. The same reference offered the surgical results from 11 cases in the category of arteriovenous anomaly: 1 patient was worse, 7 experienced no change, and 1 received slight benefit. In 2 cases no statement was made concerning result. Among 3 patients with telangiectasis treated surgically, evacuation of an intramedullary hematoma brought improvement in 1, the same procedure gave no benefit in the second, and laminectomy and decompression failed to help in the last.

Scoville, in 1948, excised an arteriovenous lesion from the conus region in a patient who presented a pain problem and complained of occasional difficulty with micturition and periodic diffuse weakness of his legs; however, the neurologic findings had been negative. Complete subarachnoid block had been indicated on myelography with oxygen. Six years after operation the patient's only disability was a slight limp and a sensory loss in the right lower leg and the saddle area. Trupp and Sachs coagulated or ligated vessels, or did both, in 7 cases of vascular anomaly. Improvement was claimed for 2 patients after coagulation, but a third was worse. In 3 cases no change resulted from the procedures mentioned, and the outcome in 1 case was not stated. Epstein, Beller, and Cohen described 6 cases of vascular malformations in which laminectomy and decompression were carried out. One patient was worse; 3 were unchanged by surgery (2 of these later becoming worse); 1, with a pain problem, was relieved of pain; and 1 patient received some benefit. In this last, an "almost complete" subarachnoid block had been indicated by manometry and myelography.

a b

FIG. 7. a, Myelogram showing vascular anomaly comprised of small vessels involving the thoracic sector of the spinal cord. b, Same case. Transosseous venogram showing so many venous channels that the normal ones cannot be differentiated from the abnormal.

Brion, Netsky, and Zimmerman, in reviewing 31 cases of a clinical appearance of transverse or diffuse myelitis, found that in 9 cases the lesion of the cord was a myelomalacia secondary to malformation of vessels of the spinal cord. Among 5 patients in whom laminectomy and decompression were carried out, 3 were worse and 2 experienced no change after operation.

Bassett, Peet, and Holt reported 8 cases treated surgically. Ligation and excision were carried out in 5 cases, with improvement in 3 (1 of them essentially a pain problem) and no change in 2. Laminectomy and decompression were employed in 1 case without benefit. In 2 cases, of which it is not stated whether anything more than laminectomy and decompression were done,

TABLE I.—SURGICAL RESULTS IN 23 CASES OF VASCULAR ANOMALY OF THE SPINAL CORD

Anomaly and result	*Laminectomy and decompression*			
	Alone	*With ligation and excision*	*With ligation and coagulation*	*Totals*
Venous				
Unchanged.....	4	1	–	5
Worse.....	3	2	1	6
Arteriovenous				
Unchanged.....	4	2	–	6
Worse.....	2	1	1	4
Telangiectasis				
Unchanged.....	1	–	–	1
Worse.....	–	–	1*	1*

*No ligation in this case.

1 patient was worse and 1 experienced no change.

Newman (9) reported that among 11 patients treated by laminectomy and decompression, no improvement was noted in any. His review of literature on the subject referred to 172 published cases. His appraisal stated that only 7 of 67 patients were benefited by laminectomy and decompression, and those only slightly. Benefit from ligation or coagulation, or both, of abnormal vessels was claimed for 7 patients, the total number so treated being not stated.

Gross and Ralston presented a series of 10 patients treated by laminectomy and decompression and reported 2 patients improved at the time of discharge, 5 slightly improved, 1 unchanged, 1 worse, and 1 dead.

Results of surgery in our series. Surgery was carried out in 23 of the 32 cases reviewed in our own series, with the results given in Table I. It will be seen that no improvement was recorded.

DISCUSSION AND CONCLUSIONS

Our experience with surgery in these cases parallels that in the majority of reports of relatively large series of cases. Wyburn-Mason concluded that laminectomy and decompression had little if anything to offer and that both excision and ligation were fraught with danger of cutting off the blood supply to other parts of the cord and of producing thrombosis in the intramedullary vessels and aggravating the symptoms. Newman (9) stated that British neurosurgeons have found the results of surgery disappointing.

When improvement has been attributed to surgery, several qualifications might properly be required. (1) Has the follow-up period been long enough to be significant? In a number of reported cases improvement seemed to follow surgery, but after a time the patient's condition deteriorated. It is clear that surgery does not prevent further attacks with devastating neurologic effects. (2) Is the improvement alleged to follow surgery one of practical importance to the patient? In many reported cases of improvement the alleged benefit seems to have been minor and largely subjective. (3) Is it not likely that improvement noted some time after surgery is the result of the natural history of the disease? Often the disease is characterized by a progression of symptoms through a series of episodes, at first possibly with almost complete recovery between attacks, though sooner or later the damage becomes permanent.

In our series, 10 of 23 patients treated surgically were worse thereafter. This result was of little consequence to some, because they were badly crippled beforehand. In other cases, however, the loss resulting from surgery was a very significant one, such as loss of bowel and bladder control. Again, one might claim with some justification that the worsening, in some cases at least, should be attributed not to surgery but to the natural course of the disease. Nonetheless, some patients were worse immediately following surgery and never regained their preoperative status.

Are there, then, any indications for surgery in these cases? We believe that there are three circumstances that justify it, and in these circumstances we advise operation.

1. Presence of persistent, intractable pain. Pain is present in most cases during the episodic manifestation of the disease but usually is not persistent. In all probability,

it is due to pressure of large abnormal vessels on the nerve roots. In a number of reported cases posterior root section, or decompression alone, has resulted in relief of pain. It seems that posterior root section should be contemplated if pain is severe and intractable.

2. Progressive neurologic loss, with manometric and myelographic indication of complete subarachnoid block. Even though the characteristic myelographic picture of vascular anomaly is unequivocally demonstrated, it is logical for a surgeon to believe that such a patient would benefit from surgical resolution of the obstruction. There is nothing in the literature to confirm or deny this supposition; and consequently, until this point can be settled, we believe that laminectomy and decompression with release of the block should be carried out. In a recent case, however, acting upon these considerations, we achieved no improvement by extensive opening of the dura, which appeared very tight.

3. Diagnosis of intramedullary hematoma. When this diagnosis is made, evacuation is indicated. Odom, Woodhall, and Margolis report 2 such cases resulting from bleeding by capillary hemangioma in which improvement followed evacuation of the intramedullary clot. The history of catastrophic involvement of the cord in addition to myelographic evidence of enlargement of the cord should suggest the diagnosis.

Teng and Shapiro claim beneficial results from section of dentate ligaments in cases of arterial anomaly of the spinal cord, but we have had no experience with this procedure.

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ELECTIVE VERSUS DELAYED NECK DISSECTION IN CANCER OF THE LARYNX

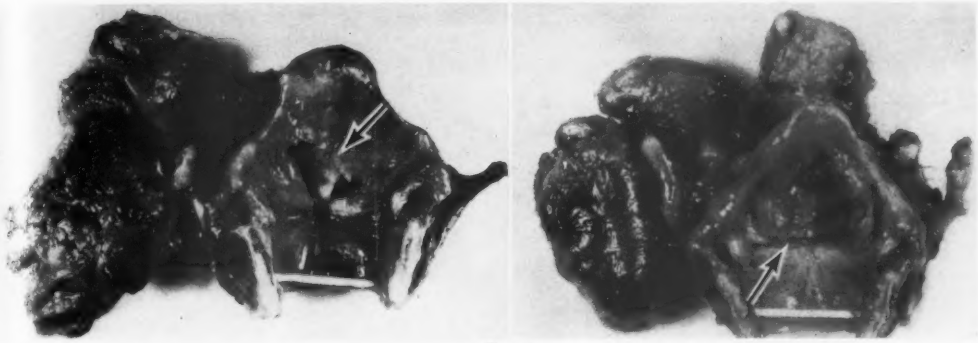
F. JOHNSON PUTNEY, M.D., Philadelphia, Pennsylvania

METASTASIS to the regional cervical lymph nodes occurs frequently in carcinoma of the larynx when areas outside of the vocal cords are involved. It occurs less commonly in those lesions limited to the vocal cords in which there is no evidence of extension to other parts of the larynx. The presence of metastasis to lymph nodes is more closely related to the prognosis than is the size or duration of the primary lesion. Block dissection of the neck is the best method of treatment for regional lymph node metastasis and the only controversy is in regard to the timing, i.e., should it be performed as an elective procedure before there is clinical evidence of lymph node involvement or as a therapeutic procedure at the time that palpable lymph nodes develop. The ultimate decision must rest upon the 5 year survival rate to determine whether the figures for those in whom prophylactic neck dissection was performed are superior to those in whom this procedure was not carried out.

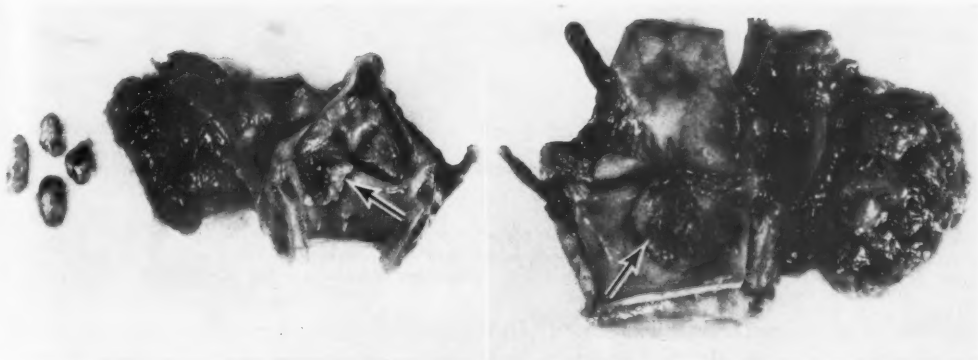
Rouvière demonstrated that the lymph drainage from the larynx enters two main streams, the supraglottic and infraglottic collecting chains which are divided by the true vocal cords. Both chains drain into the internal jugular group of lymph nodes, the supraglottic by means of a pedicle near the arytenoepiglottic fold extending to the pyriform fossa and through the thyrohyoid membrane along the course of the superior laryngeal vessels to reach the internal jugular and subdigastric nodes, and the infraglottic group through the cricothyroid node on the cricothyroid membrane by way of the pretracheal nodes or by drainage through the thyroid lobe to reach the internal jugular lymph node chain.

Edema and induration of the neck, necrosis of cartilage, fixation of the laryngeal structures, and ulceration increase the chances of lymphatic invasion and distant spread. In cases of cancer of the larynx, palpable cervical lymph nodes are a definite indication for neck dissection even though I found that in 34 per cent of cases enlarged lymph nodes were not due to metastatic disease (1). Generally, the first site of metastasis is in the cervical lymph nodes on the side of the primary involvement, and the lymph node on the cricothyroid membrane is not commonly involved by cancer. Perhaps the fibrous cricothyroid membrane prevents this method of spread or the lymph drainage from the interior of the larynx is not readily directed toward this node. When the cricothyroid lymph node is invaded, subsequent spread to the cervical lymph chain may develop on either or both sides, and metastasis does not necessarily involve the side of the primary lesion.

The presence of enlarged lymph nodes is considered evidence of cervical metastasis, and biopsy is not advocated prior to the definitive surgery. The principal reason for withholding biopsy is because a false sense of security develops if an excised lymph node is reported not to contain carcinoma even though there might be metastasis to other lymph nodes clinically insignificant and evident only upon microscopic examination. Although cancer is not found in a single representative lymph node, one cannot rely entirely upon this finding as a means of determining the presence of metastatic disease. The danger of implanting tumor even when an entire lymph node is removed should not be considered lightly since the recent study of Smith, Thomas, and Hilberg demonstrated more than 25



a FIG. 1. b



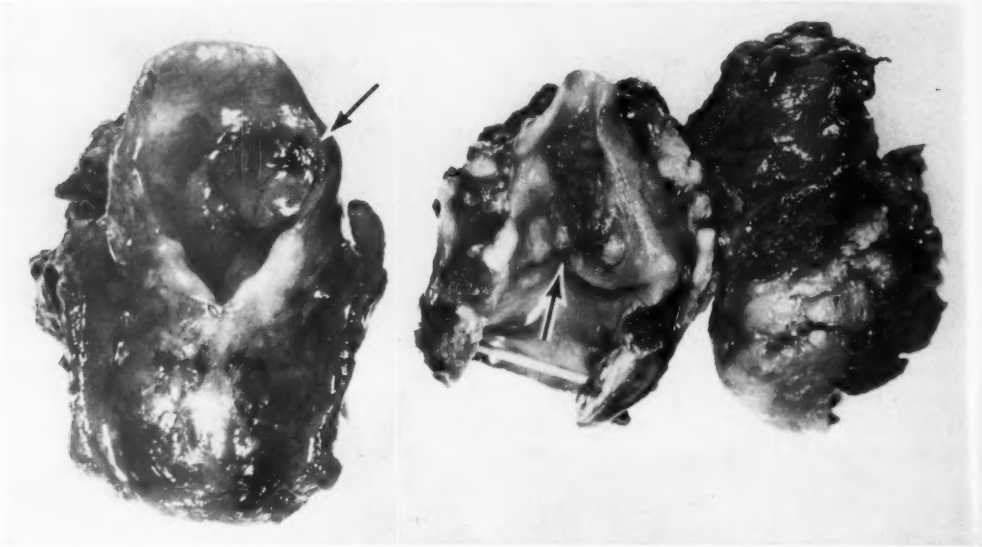
a FIG. 2. b

FIG. 1. a, Specimen shows carcinoma of epiglottis and no clinically enlarged lymph nodes of neck. Two positive nodes were found histologically in the neck. The patient died within 2 years. b, Large ulcerative carcinoma penetrating through epiglottis and vallecula into base of tongue. No metastatic lymph nodes were present histologically in the primary neck dissection or the secondary neck dissection performed after a 3 week interval on the opposite side of the neck. Patient survived for more than 5 years.

FIG. 2. a, Subglottic carcinoma in which no cervical lymph nodes were palpable, yet at operation 4 enlarged lymph nodes behind the internal jugular vein contained metastatic carcinoma. b, More extensive subglottic carcinoma in which no positive lymph nodes were found on histologic study.

per cent malignant cells in fresh surgical wounds. Surgical scarring and interference with lymphatic drainage so that subsequent block dissection could not be performed as an inviolate block were lesser factors in the decision against biopsy.

Two hundred and thirty-six block dissections of the neck were performed for carcinoma of the larynx (1). Carcinoma in all portions of the larynx and in all structures contiguous with the larynx were included, and it was not possible in every instance to determine, from the laryngeal lesions, at the time of operation, the original site of the growth. There was little variation in the instance of cervical lymph node metastasis from lesions within the larynx which included lesions of the base of the epiglottis, anterior commissure, vocal cords, and ventricular band. When carcinoma was limited to the vocal cords or involved the vocal cords and ventricular band alone, it was found that 58 per cent of the patients had cervical lymph node metastasis. In lesions of the arytenoid, arytenoepiglottic fold, and vallecula, an 80 per cent incidence of cervi-



a b

FIG. 3.

FIG. 3. a, Epiglottic carcinoma with no palpable cervical lymph nodes. Metastatic carcinoma developed on the right side of the neck 6 months later and radical neck dissection was required. b, Large ulcerating carcinoma of epiglottis without metastasis to cervical lymph nodes.

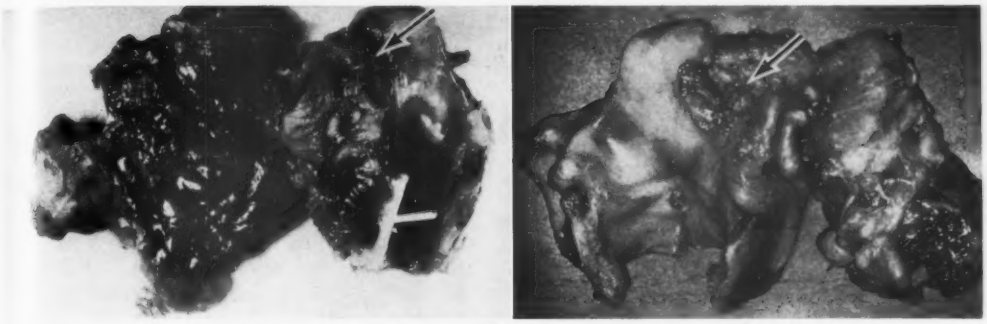
cal lymph node metastasis was noted. In some cases, positive lymph nodes were present even though the lymph nodes were small and appeared to be clinically innocuous (Fig. 1). Another feature was that the palpable lymph nodes sometimes did not contain carcinoma, whereas one that was smaller and not palpable did contain cancer (Fig. 2).

In 33 per cent of the patients in this series, metastatic cancer developed in the cervical lymph nodes after laryngectomy had been performed even though lymph nodes were not clinically palpable. In 26 per cent of 62 patients with cancer of the larynx in whom there were no palpable lymph nodes but in whom laryngectomy was combined with dissection of the neck on the involved side, histologic evidence of cervical lymph node metastasis was found.

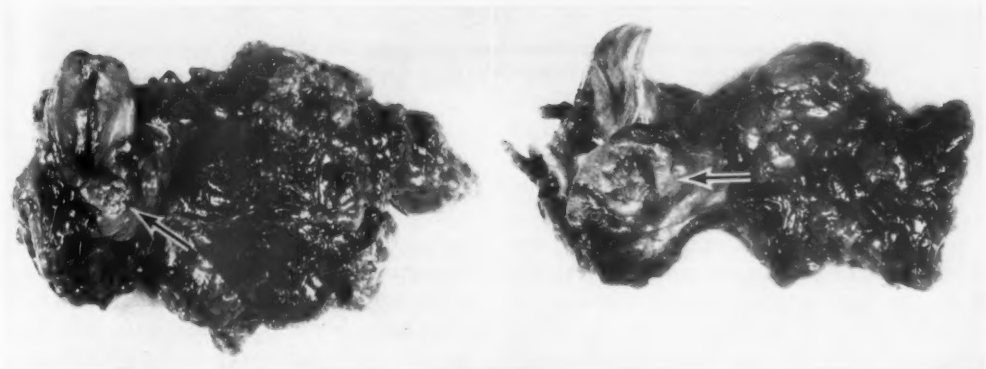
When the cases of late detection of metastasis to cervical lymph nodes are combined with those of microscopic evidence of cancer in the lymph nodes without clinical manifestations, 40 per cent of all of the patients with cancer of the larynx had cancer or it subsequently developed in the cervical lymph nodes when there was no clinical evidence of lymph node enlargement at the time of operation. With a 40 per cent incidence of cervical metastasis in nonpalpable lymph nodes, elective neck dissection could be justified in all cases of cancer of the larynx, for the 60 per cent in whom needless neck dissections were performed would not be materially jeopardized as far as mortality, morbidity, or subsequent disability was concerned.

CONTRAINDICATIONS TO NECK DISSECTION

Uncontrolled or uncontrollable primary lesions or distant metastasis are absolute contraindications for neck dissection, but relative contraindications also exist. Patients in severe poor health or in debilitated states may not be candidates for neck dissection, not primarily because they may succumb to operation but because their life expectancy



a FIG. 4. b



a FIG. 5. b

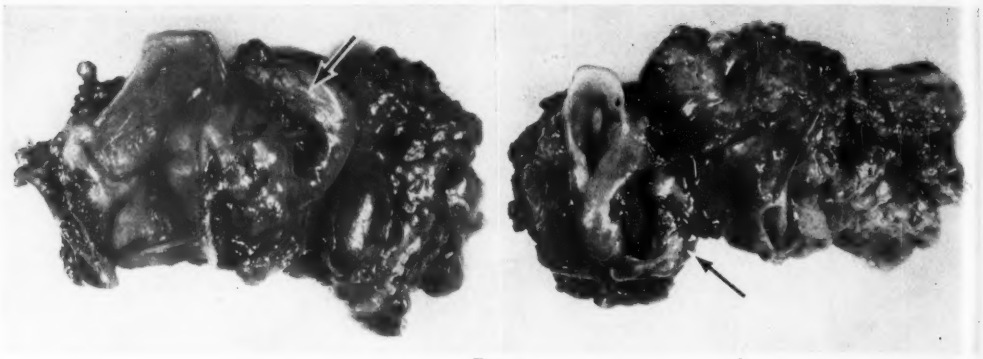
FIG. 4. a, Lesion involving the epiglottis with extension to the base of the tongue and lateral pharyngeal wall. No cervical lymph nodes were palpable preoperatively, but 3 positive nodes were discovered histologically in the elective neck dissection specimen. b, Carcinoma involving the epiglottis, vallecula, and base of tongue in which no metastatic lymph nodes were found at neck dissection.

FIG. 5. a, Carcinoma of posterior surface of larynx and pyriform fossa with many positive lymph nodes in cervical chain. b, Almost identical lesion in size and position with neck nodes negative for carcinoma.

from other medical standpoints does not warrant radical therapy. Highly undifferentiated tumors tend to develop widespread metastasis early in the course of the disease, and a thorough search should be conducted for metastasis before deciding upon radical treatment. However, even in instances of undifferentiated tumors when the primary lesion has disappeared and no distant metastasis has been found, the remaining disease in the lymph nodes should be treated by neck dissection. Surgical treatment is contraindicated when the lymph node capsule has perforated, as evidenced by fixation of invasion of adjacent structures, and is of doubtful value in the presence of bilateral or contralateral firm cervical lymph node metastasis. In the latter instance, radical operation should be reserved for slow growing tumors if there is definite knowledge that the tumor has been present for a long period of time. Involvement of vital structures such as the carotid artery makes the prognosis more grave but does not necessarily indicate inoperability.

DELAYED NECK DISSECTION

For 30 years prior to 1950 a conservative policy was followed at the Memorial Hospital, New York, regarding the treatment of



a FIG. 6. b

FIG. 6. a, Necrotic carcinoma of pyriform fossa with metastasis to cervical lymph nodes. b, Similar necrotic carcinoma of pyriform fossa without cervical lymph node metastasis.

metastatic cervical lymph node carcinoma by either surgery, irradiation, or both and only if and when the lesion was clinically evident. If cervical lymph node metastasis can be discovered and treated early, no undue risk to the patient will result and, therefore, needless surgery can be avoided. In patients who can be followed up, the delay of a few weeks or months may not materially influence the survival rate because neck dissection can be successfully performed at the time of evident lymph node metastasis. If a careful follow-up is carried out 95 per cent of the patients can be seen and the disease will be discovered as soon as cervical lymph nodes become palpable. Neck dissection can then be performed and the patient's chances for cure are not jeopardized. At active follow-up clinics, cervical lymph node metastasis can be discovered soon after it occurs and prompt neck dissection is curative.

The operative mortality in neck dissection has been estimated to be as high as 7 per cent, and higher when carried out by a surgeon performing only an occasional neck operation. While the mortality rate in the hands of a trained laryngologist is negligible except in cases of concomitant disease, when this operation is performed by a surgeon unfamiliar with the anatomy of the neck or the surgical techniques employed in this region the mortality rate is increased.

In 33 per cent of patients with no clinical evidence of cervical lymph node metastasis on admission cancer developed after laryngectomy; therefore, if neck dissections were carried out on all patients approximately two-thirds would be unnecessary. Thirty-seven per cent of the patients on whom neck dissections were performed only after the lymph node metastasis was evident survived 5 years. If more than one-third of the patients can reach a 5 year survival period after delayed neck dissection in cancer of the larynx, is it necessary to perform this surgery before metastasis to the lymph nodes of the neck is clinically evident?

ELECTIVE NECK DISSECTION

In 26 per cent of the 62 patients with clinically normal lymph nodes, there was histologic evidence of metastatic cancer (Fig. 3). In these 62 cases in which lymph nodes were not palpable, unilateral block dissection was performed as an elective procedure either because of the extensiveness of the laryngeal lesion or because it was not confined to the vocal cords or ventricular bands (Fig. 4). Serial sections of the extirpated lymph node block were not routinely taken and would probably have resulted in an even higher percentage of positive reports. In these patients with microscopic metastatic cancer of the lymph nodes not

palpable before operation, the primary lesion was on the vocal cords and ventricular band in only 2 intances, 12.5 per cent. The greatest numbers of positive lymph nodes were found in those regions beyond the confines of the vocal cords, epiglottic or subglottic lesions (Fig. 5).

When neck dissection was combined with laryngectomy the mortality did not increase and the morbidity increased only slightly for the mortality rate in either laryngectomy or laryngectomy combined with radical neck dissection was less than 2 per cent.

Some patients fail to return for follow-up examinations and lose their chance for cure if subsequent lymph node metastasis develops. Patients living at a distance may not return periodically to be followed up and, even in the hands of their own physicians, cervical lymph node metastasis may become quite extensive before it is recognized and the patient returns for treatment. If all patients were seen by the operating surgeon as soon as the smallest enlarged lymph node appeared, delayed neck dissection would offer a higher rate of cure. It is not always possible to tell which patients will return for frequent and prolonged follow-up visits; therefore, prophylactic neck dissection removes the possibility of lymph node metastasis developing and remaining untreated in the small group of patients who may not return for subsequent examination.

BILATERAL NECK DISSECTION

Difficulty was often encountered in selecting the side for block dissection when no lymph nodes were palpable and when the lesion was situated in the midline such as the epiglottis, anterior commissure, and postcricoid area. In the midline lesions, particularly of the epiglottis, neck dissection should be done bilaterally but not simultaneously. Both the morbidity and mortality rates are increased when bilateral dissection of the neck with laryngectomy is performed in one stage because the concurrent ligation of both internal jugular veins increases the morbidity rate. Simultaneous bilateral neck dissection and laryngectomy were performed in 15 cases with no deaths but with an increase in morbidity. Edema and cyanosis of the soft tissues about the face and neck developed accompanied by severe headache and malaise. Drainage of cerebrospinal fluid by lumbar puncture relieved the increased pressure and stabilized the central nervous system in some cases.

FIG. 7. Relatively small carcinoma of the vocal cord in which lymph node metastasis to the opposite side of the neck developed within 3 months after laryngectomy.

When there were no palpable lymph nodes, dissection of the neck was performed with laryngectomy on the side of the greater primary involvement, and the opposite cervical lymph nodes were removed at a later date (Fig. 6). When lymph nodes were palpable, the initial dissection of the neck was performed on the involved side followed by extirpation of the contralateral cervical lymph nodes at a later time. By allowing a time lapse between the neck dissections, the vascular system became adjusted to the unilateral deficiency in blood supply and compensated better for the subsequent change in vascularity when the contralateral jugular vein was removed. The time elapsing between the primary neck dissection and the secondary operation varied from 3 to 6 weeks. The second operation was performed after the primary operative wound was well

healed. Removal of only 1 internal jugular vein in bilateral neck dissections is not good surgical practice since the operation is incomplete and lymphatic vessels are left.

In addition to midline lesions, bilateral dissection of the neck was performed in cases of long-standing or extensive local disease, and in those with bilateral palpable lymph nodes. In some cases, cervical lymph nodes contained cancer bilaterally while in others carcinoma was present on the side of greater involvement. In still others, the lymph nodes were involved on the side of the lesser primary involvement (Fig. 7).

SUMMARY

In a series of 236 neck dissections performed for carcinoma of the larynx, with and without palpable cervical lymph nodes, metastatic carcinoma was found in 55 per cent. In 33 per cent, cervical metastasis developed after laryngectomy even though no lymph nodes were palpable at the time of the primary operation. Secondary neck dissection was performed in this group with a 5 year survival rate of 37 per cent. Since 63 per cent of the patients who had block dissection after clinically evident cervical lymph node enlargement subsequently died from the disease, the possibility of salvaging an added number by prophylactic neck dissection should be considered.

Prophylactic dissection of the neck was performed in conjunction with laryngectomy in 62 patients with no palpable lymph nodes, and in 26 per cent cancer was proved histologically. Needless neck dissection cannot be weighed against survivors who are alive because of prophylactic block dissection. Elimination of metastasis to cervical lymph nodes in approximately one-quarter of patients before it is clinically evident gives this group a greater chance of cure than the group in which additional time is allowed for lymph nodes to become palpable.

When the laryngeal lesion is situated in the midline, is extensive, or involves structures outside of the larynx proper, two stage bilateral neck dissection is indicated, the first block dissection being performed on the side with palpable lymph nodes or, if no lymph nodes are palpable, on the side of greater involvement. After an interval of several weeks, the contralateral neck dissection can be carried out.

In reviewing all of the factors of elective versus delayed neck dissection in cancer of the larynx it would seem that elective neck dissection should be performed in all cases of cancer of the larynx when the lesion is not limited to the vocal cords or if there is minimal involvement of the ventricular bands.

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URINARY DIVERSION IN PELVIC EXENTERATION

JOHN J. MURPHY, M.D., F.A.C.S., and JOHN J. MIKUTA, M.D., Philadelphia, Pennsylvania

PELVIC EXENTERATION has achieved a justifiable position in the management of malignant pelvic lesions during the past decade. The most encouraging results from this type of surgery have been obtained in the treatment of patients with cancer of the uterine cervix in whom radical hysterectomy or the usual therapeutic doses of irradiation have failed. Results with pelvic exenteration, reported most extensively by Brunschwig (2, 3, 5-7) and Parsons (11, 12) and their associates reveal that immediate and long term survival are possible and that many of the patients return to a happy and useful life. The emphasis has shifted from palliation to attempted cure, and today the operation is rarely performed unless there is a reasonable chance that all of the gross tumor is limited to the pelvis and can be removed.

The effort to produce curative results has focused an increasing amount of attention upon the problem of diversion of the urinary stream necessitated by removal of the bladder. The ideal solution would be a reservoir which would permit intermittent evacuation of urine under voluntary control and which would protect the upper urinary tract from stasis and infection. A practical operation yielding such a result is yet to be found. The most promising advance to date has been the utilization of isolated bowel conduits as proposed by Bricker in 1950. A modification of this method has been used in this clinic.

The total experience with isolated bowel conduits for urinary diversion at the Hospital of the University of Pennsylvania as of June 1960 consists of 74 patients (Table I). The procedure has been carried out in 26 patients with pelvic exenteration, in 23 patients with "useless bladders," in 13 patients with cystectomy, in 9 with intractable vesicovaginal fistulas, and in 3 for palliative reasons. The follow-up period varies from 3 months to 8 years. Eighty-three per cent of the patients have been followed up for more than 1 year. In 44 patients, the most recent evaluation of renal status shows no change from preoperative examinations; 18 show definite improvement; and 7 are judged to be worse. Electrolyte imbalance has not been a problem in any of these patients.

From the Division of Urology, Department of Surgery, the Department Obstetrics and Gynecology, and the Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania, Philadelphia.

TECHNIQUE

A segment of ileum or sigmoid colon of sufficient length to reach both ureters and the abdominal skin without tension is isolated from the continuity of the gastrointestinal tract (Fig. 1 a and b). It is important to avoid an excessive length of bowel, since absorption of urinary constituents occurs and is related to the area of intestinal mucosa exposed to the urine as well as to other factors, as we have found (9). The segment of bowel is carefully chosen to avoid areas which may have received large amounts of irradiation during previous treatment for malignant disease. The mesentery is divided sufficiently to allow the bowel to be brought easily to the ureters and to the external abdominal wall. It should not be divided more than absolutely necessary because of the danger of interfering with the blood supply of the bowel. The proximal end of the isolated segment is closed with two layers of No. 3-0 chromic catgut and one of silk. The ureters are anastomosed to the posterior side of the bowel with a single layer of interrupted No. 5-0 chromic catgut by the elliptic method of Nesbit. The distal end of the intestinal segment is brought

TABLE I.—TOTAL EXPERIENCE, JUNE 1960

Indication	No. pts.	Follow-up period: 1 yr.	1–3 yrs.	3–8 yrs.	Renal status: Imp.	Unch.	Worse
Pelvic exenteration...	26*	6	14	6	2	17	3
"Useless bladder"	23	3	7	13	12	9	2
Cystectomy.....	13†	1	8	4		11	1
Vesicovaginal fistula.....	9	2	0	7	4	4	1
Palliation.....	3	0	1	2		3	
Total.....	74	12	30	32	18	44	7

*Four patients died in the immediate postoperative period.
†One patient died in the immediate postoperative period.

TABLE II.—PELVIC EXENTERATION, JUNE 1960

Indication	No. pts.	Isolated segment: Sigmoid	Ileum	<1 yr.	Survival: 1–3 yrs.	3–5 yrs.	Renal status: Imp.	Unch.	Worse
Ca.cervix	20	5	15	9	7	4	2	11	3
Ca. rectum	2	1	1		1	1		2	
Ca. prostate	2		2		1	1		2	
Ca. anus	1		1	1				1	
Ca. urethra	1		1		1			1	
Total	26	6	20	10	10	6	2	17	3

through an excised ellipse of skin, fascia, muscle, and peritoneum at a convenient site in the lower abdomen. The stoma must be placed so that successful application of an adherent collecting device is feasible. The open edge of the bowel is sutured to the skin edge with interrupted sutures of fine cotton. When a segment of ileum has been used as a conduit, continuity of the bowel is re-established by end-to-end anastomosis. Some patients in whom total exenteration has been carried out have a redundant sigmoid colon, a portion of which may be isolated for use as a urinary conduit. This saves operating time, since the proximal bowel is brought out as an end colostomy, and the need for small bowel anastomosis is obviated. The appliance or a rubber dam is attached to the cutaneous stoma at the end of the operation.

RESULTS

In the past 6 years, 26 pelvic exenterations have been performed at the Hospital of the University of Pennsylvania for pelvic malignant disease (Table II). In 6 patients, an isolated segment of sigmoid colon was used for urinary diversion, and a segment of ileum was employed in the remainder. Twenty of the procedures were carried out for carcinoma of the cervix which was resistant to or recurrent after radiation therapy. Two were carried out for carcinoma of the rectum, 1 for carcinoma of the urethra, 1 for carcinoma of the anus, and 2 for carcinoma of the prostate. Four patients died in the immediate postoperative period, and 13 died from 4 months to 6 years later with tumor recurrence. Of the remaining 9, 1 has suffered mild but recurrent pyelonephritis. None has exhibited azotemia or electrolyte disturbances. A review of the excretory urograms reveals 17 to be unchanged from the preoperative examinations, 2 are definitely improved, and 3 are classified as worse.

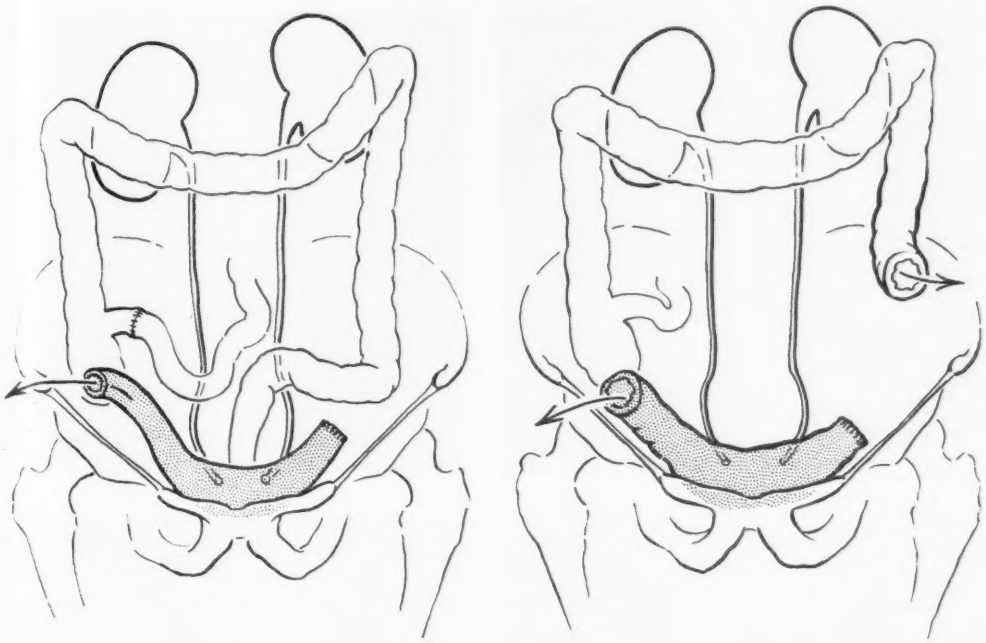
REPORTS OF PATIENTS

The following histories are typical of the majority of patients subjected to exenteration in this series.

Patient 1 was a 40 year old female found to have a squamous cell epithelioma of the cervix in June 1957. The lesion was classified as stage II, International. A course of external roentgen therapy using conventional sources was completed within 6 weeks and a modified Manchester system of intracavitary radium was then applied. The dosage was considered entirely adequate for the lesion. The patient was seen at monthly intervals, and the cervix appeared to be healing until December 1957, when vaginal bleeding was noted by the patient and the cervix was found to be involved by an ulcerating lesion which biopsy proved to be a recurrent squamous cell carcinoma.

In January 1958, anterior pelvic exenteration was carried out. Urinary diversion was accomplished by anastomosis of both ureters to an isolated segment of ileum. An excretory urogram prior to operation revealed no abnormalities (Fig. 2). The patient's postoperative course was completely satisfactory and re-evaluation 30 months after operation showed no change in the pyelographic appearance (Fig. 3) or electrolyte or clinical status.

Patient 2 was a 36 year old female treated for a carcinoma of the cervix, stage III by International classification, from March through May 1955 by external roentgen and intravaginal cone therapy. In August 1955 she was readmitted to the University Hospital where the lesion was found to be extending to the left lateral pelvic wall. Further irradiation was given with bilateral parametrial radium needle implantation. There appeared to be some response to



a b

FIG. 1. Diagram of anastamosis of both ureters to, a, isolated segment of ileum and, b, sigmoid colon.

the second course of therapy and a total pelvic exenteration was considered feasible. This was accomplished in October 1955. The ureters were diverted to an isolated segment of sigmoid colon. An excretory urogram 2 months prior to operation showed slight impairment of function of the right kidney and no apparent function of the left (Fig. 4). The most recent urographic study 4 years after operation reveals the right kidney to be unchanged in appearance, whereas a small but functioning kidney can be seen on the left side (Fig. 5). This patient has had no evidence of urinary tract infection or electrolyte disturbance.

DISCUSSION

Methods of managing the urinary tract after removal of the bladder during pelvic exenteration have been of various types. Brunschwig and Daniel (5) have used cutaneous ureterostomy as well as ureterosigmoidostomy, either as a wet colostomy or above an intact anal sphincter. Of 84 patients so managed who failed to leave the hospital, 13 died of urinary tract complications. A long term follow-up of 10 patients similarly treated who lived from 4 to 7½ years after operation revealed considerable difficulty with urinary stasis and electrolyte imbalance (4). This was especially true in the patients in whom the urine was diverted to the colon above an intact anal sphincter. Parsons and Taymor (12), using similar forms of urinary diversion, reported recurrent episodes of pyelonephritis in 9 of the 16 patients living from 2 to 6½ years postoperatively. They report the employment of transverse colostomy proximal to the ureterosigmoidostomy to free the left side of the colon from the flow of feces. This procedure apparently decreases the incidence of renal infection but leaves a longer segment of bowel than is desirable from which urinary constituents may be absorbed. Results with cutaneous ureterostomy have been discouraging because of stenosis of the stoma and the need for

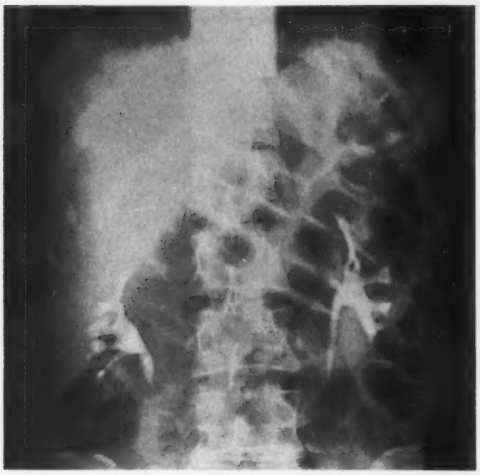


FIG. 2.

FIG. 3.

FIG. 4.

FIG. 5.

FIG. 2. Preoperative urogram of Patient 1.
FIG. 3. Urogram 30 months after diversion to isolated ileum segment.
FIG. 4. Preoperative urogram of Patient 2. Note lack of visualization of the left kidney.
FIG. 5. Urogram 4 years after operation in Patient 2, showing left kidney functioning.

indwelling tubes. Douglas and Sweeney reported that 20 of 23 patients subjected to exenteration had postoperative hydronephrosis and that 18 of this group had pyelonephritis. Most of these patients had urinary diversion through a cutaneous ureterostomy, whereas the remainder had ureterosigmoidostomy.

Wawro and Howe performed ureteroileostomy with exenteration on 21 of 44 patients. Their results strongly favor continuation of the use of this procedure.

There is no question that urinary diversion to an isolated intestinal segment adds to the length of the operative procedure. An additional 2 hours is usually required for isolation of the intestinal segment, anastomosis of the ureters, and formation of the abdominal stoma. If the patient's condition is not satisfactory after the pelvic dissection has been completed, the urinary stream might be diverted temporarily to the skin, and isolated intestinal segment diversion performed at a later date.

When total exenteration has been performed, it may be feasible to isolate a portion of the sigmoid colon for use as a urinary conduit, thereby obviating the need for a small intestine anastomosis. This decreases the operating time as well as the duration of postoperative intubation and parenteral feeding. If the sigmoid is not redundant and a satisfactory colostomy cannot be made without mobilization of the splenic flexure of the colon, the use of an isolated segment of ileum is preferred. In all anterior exenterations, an isolated segment of ileum is used.

SUMMARY

The operation of pelvic exenteration is now performed primarily in an attempt to cure malignant lesions for which no other therapy is available. Successful eradication of the cancer may be completely nullified by complications associated with diversion of the urine. The results reported herein indicate that the use of isolated bowel conduits prevents recurrent pyelonephritis, electrolyte imbalance, and progressive renal damage and permits an honest evaluation of the exenteration procedure.

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EDITORIALS

SURGERY OF THE HEAD AND NECK

OLIVER H. BEAHRS, M.D., F.A.C.S., Rochester, Minnesota

THE HEAD AND NECK constitute an anatomic region in which a large variety of tumors occur. Since the various types of lesions are treated in many ways, it is extremely important that the differential diagnosis be carefully considered. If this is done, the surgeon and the patient can be properly prepared for the surgical procedure of choice. Rarely should an operation on the neck be considered an office procedure. It should be carried out in the operating room with adequate preparation so that the surgeon will be able to extend the operation as he may find it indicated on the basis of the character of the tumor removed. Such a procedure presupposes the availability of a surgical pathologist trained in the technique of making and examining frozen sections. This plan offers the patient the best treatment and the best chance of cure if the lesion is malignant. The primary reason for removal of any tumor is to determine the malignancy or benignancy of the lesion.

If immediate pathologic interpretation is not available, the surgeon must weigh the increased risk to the patient involved in performance only of excisional biopsy with the scheduling of definitive surgical treatment at a later time. Needle biopsy might be a preferred procedure in these circumstances, to be followed by wide excision of the needle tract if the lesion proves to be malignant.

From the Section of Surgery, Mayo Clinic, Rochester, Minnesota.

Any surgeon operating on the neck should be thoroughly familiar with the anatomy of the area, for only if he has a sound understanding and knowledge of this region will the complications and morbidity be held to a minimum. Every structure should be known to the surgeon before he begins retraction or division. The incision always should be made in a linear manner and positioned in such a way that it can be extended properly to facilitate a more extensive procedure if such is seen to be needed. Too often a surgeon operating secondarily has to deal with a poorly placed incision or one which was made in the wrong direction. Because the head and neck are exposed areas of the body, the cosmetic appearance of the incision is of greatest importance.

Finally, any surgeon who operates in the area of the head and neck should be thoroughly acquainted with lesions occurring in this area and the natural history of such lesions. A surgeon's viewpoint should be flexible: he should select the operation which is indicated on the basis of all factors related to the lesion. For instance, metastatic papillary adenocarcinoma of the thyroid gland in the lateral aspect of the neck only occasionally needs to be treated by radical dissection of the neck. Modified dissection of the neck with removal of the involved group or groups of nodes and preservation especially of the sternocleidomastoid muscle leaves a much better cos-

metic result than the radical operation and offers the patient an excellent chance of cure, 97 per cent after 5 years and 89 per cent after 10 years. On the other hand, a squamous cell carcinoma which has metastasized from an intraoral primary lesion always should be treated by a radical dissection of the neck, with en bloc excision of the metastatic lesion and as much of the adjacent tissues as can be sacrificed. Both lesions are malignant, but the course of each is different. A similar corollary can be made between mucoepidermoid carcinoma of the parotid gland and a highly neoplastic adenocarcinoma, the former requiring subtotal or total conservative parotidectomy, with preservation of the facial nerve, and the latter requiring total radical parotidectomy.

The foregoing comments do not apply exclusively to surgery of the head and neck but seem worthy of mention, since tumors in this anatomic area often are badly mismanaged. The golden opportunity to cure the patient who has a lesion in this area, as is true of the one with a lesion elsewhere in the body, is at the first operation, well planned and well executed.

THE GUESS AND THE GAMBLE

RICHARD H. OVERHOLT, M.D., F.A.C.S., Boston, Massachusetts

WHEN THE ALARM is given by the red flag of blood or the sharp stab of pain, the response is usually immediate action. Serious pulmonary disease, unfortunately, usually creeps up insidiously. Roentgenologic chest screening may turn up evidence of abnormality which is not supported by either symptoms or direct objective findings. Also, if an obvious abnormality is discovered upon examination, concern over its presence is often related to size. The smaller the process, the less the apprehension, but the greater the invitation to procrastination.

The high contrast of the air-filled lung permits recording of density changes not only of large and medium size, but also of small size, measured even in millimeters. Often the shadow is round and approximates the area of a shadow of a dime, nickel, quarter, or fifty cent piece, hence the term "coin lesion."

The history is noncontributory in many cases. Nonexistent symptoms are combined with a negative physical examination. The conventional search for clues is fruitless. The substance that has produced the roentgenologic shadow is out of range of bronchoscopic vision. Sputum or aspirated secretions usually fail to yield either tumor cells or tubercle bacilli. It is assumed that the discovery film was followed up with angulated positions for precise localization and that possible calcium deposits were not found in these views or laminagrams.

The only telltale evidence of potential lung trouble is the abnormal area of roentgenologic density. In roentgenologists' offices, consultation rooms, or conferences, various opinions are expressed. Then the guessing game begins. In times past, both roentgenologist or medical chest specialists, long conditioned by the slow turn of events in tuberculosis or nonspecific types of localized inflammatory processes, were inclined to defer a decision. Time was relied upon to register enlargement or regression in serial films. With the incidence of tuberculosis fading and cancer increasing, management practices must change. Intervals of weeks may be justified; a waiting period of 2, 3, or 6 months is not.

The cancer potential of each shadow must be weighed as soon as phantom shadows or artifacts have been dismissed. The cancer potential will vary with respect to sex, age, and smoking history. The yield of cancer in all adults, with an unexplained solitary single density, will run between 30 and 50 per cent. If excision is carried out soon after the discovery film, over one-half of the patients with silent pulmonary cancer will show no demonstrable extension beyond the original site. Furthermore, 5 year survival figures for localized cancer produce rates which have exceeded 50 per cent.

The operative mortality for localized cancer is extremely low—1 per cent, plus or minus. This risk and the cancer potential of the coin lesion should be frankly discussed and honestly balanced for the patient. There is little room for confusion or hesitation. A mass in the lung should be managed like a mass in the breast. The direct approach must be recommended because it is quick, sure, and safe. Procrastination with a coin lesion is an unfair gamble. It is the patient, not the doctor, who plays this game of Russian roulette with *three bullets in the six-shooter.*

THE SURGEON AT WORK

USE OF A NEW SIMPLIFIED PLETHYSMOGRAPH IN THE CLINICAL EVALUATION OF PATIENTS WITH ARTERIOSCLEROSIS OBLITERANS

D. E. STRANDNESS, JR., M.D., H. M. RADKE, M.D., and
J. W. BELL, M.D., F.A.C.S., Seattle, Washington

A MAJOR PROBLEM in the surgical treatment of peripheral manifestations of arteriosclerosis obliterans is the selection of patients for operation. A recent survey of patients receiving treatment for arteriosclerosis obliterans at the Veterans Administration Hospital, Seattle, Washington, clearly demonstrated that clinical evaluation alone is not sufficiently accurate to predict the results of reconstructive procedures or sympathectomy or any combination of these in any given patient (4). More important for accurate evaluation, objective data are needed concerning the degree and extent of vessel involvement, the effective collateral circulation, and the vasomotor reactivity. From this knowledge, reasonable predictions of response to surgical intervention can be made. Goetz, Winsor, and Smithwick have demonstrated the value of pneumoplethysmography in this regard, and the technique has received growing acceptance as a diagnostic and prognostic method.

The purpose in this report is to describe the application of a new type of plethysmograph in the study of peripheral vascular disease problems. The instrument has several advantages, principally its simplicity of application.

METHODS

In 1953 Whitney first described a simple mercury strain gauge for the study of forearm blood flow. The gauge consists of a small caliber latex rubber tube filled with mercury. When placed about a finger or toe, pulse volume changes in the digit produce a corresponding lengthening of the gauge and its contained mercury column, thus increasing the electrical resistance of the column. This variable resistance is arranged to form one side of a Wheatstone bridge which is coupled to an alternating current bridge circuit to permit vacuum tube amplification of the resistance changes. Since the impedance of the gauge varies from a fraction of 1 ohm to 3 or 4 ohms, and the input impedance of the strain gauge amplifiers is usually in the range of 100 to 300 ohms, direct connection is not possible. Elsner and associates corrected this impedance mismatch by incorporating appropriate transformers in the bridge to match the output of the gauge to the input of the amplifier (Fig. 1). In this form, the instrument has a sensitivity such that a change in length of the gauge of only 2 microns can be amplified to produce a 1 millimeter deflection on the record. This increase in sensitivity has made it possible to detect and record small changes in digital blood flow. The mercury rubber gauges used in this study have an inside diameter of .014 inch and a length of approximately 2 inches. These fit nicely on the average finger or toe (Fig. 2).

CLINICAL APPLICATION

Examinations are performed in a room with a temperature of from 74 to 78 degrees F. The

From the Department of Surgery, Veterans Administration Hospital and University of Washington School of Medicine, Seattle.

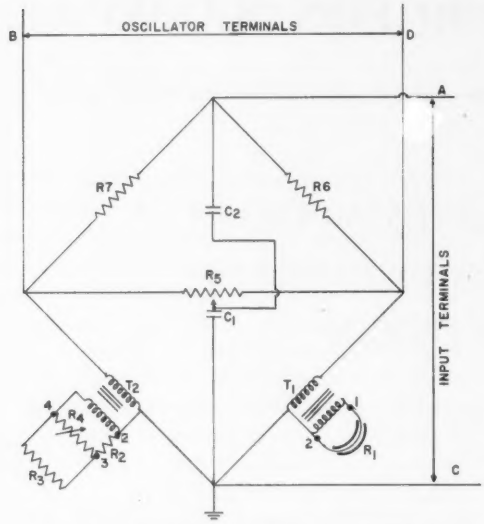

FIG. 1. The impedance matching circuit. C_1 and C_2 are 0.1 microfarad condensers; R_1, mercury strain gauge, 0.1 ohm; R_2, replaceable resistor, approximately one-half R_1; R_3, replaceable shunt for R_4, approximately equals R_1; R_4, resistance balance potentiometer 10 ohm, 3 turn Helipot; R_5, capacitance balance potentiometer, 10 ohm, wire-wound; R_6, R_7, 120 ohm resistors; T_1, T_2, matching transformers. The connections are used with a Sanborn carrier preamplifier (twin-viso model).

patient is covered with a woolen blanket and examined in the supine position. Routinely, one arm and both legs are examined. Pressure and pulse wave measurements in the arm are used as normal standards for comparison. The mercury strain gauge is placed on the distal phalanx of the finger or toe, as shown in Figure 2, and a number of observations and determinations are made.

Pressure measurements. Pneumatic cuffs are placed successively on the upper arm, the upper thigh, above the knee, below the knee, and at the ankle. At each successive level the pressure in the cuff is raised to above systolic blood pressure and gradually lowered until digital blood flow is restored as noted by a sudden increase in digital volume on the plethysmographic tracings (Fig. 3). This "opening" pressure is recorded as the systolic pressure at that level. The systolic pressure at any level in the leg is normally higher than at any corresponding level in the arm. Normally, the pressure gradient between any two successive levels is only about 10 millimeters of mercury (Fig. 3).

Pulse contour and volume. The normal peripheral pulse curve has a well defined systolic peak and a dicrotic wave on the downslope (Fig. 2). Its amplitude and form are in part dependent upon ambient temperature and the emotional "set" of the patient. Anxiety, for example, frequently produces vasoconstriction, with a decrease in pulse amplitude.

Vasomotor activity and reflexes. In normal individuals there are regular rhythmic changes in sympathetic vasomotor activity which appear as symmetric, cyclic shifts in the baseline of the plethysmographic pulse curve and which are called slow waves (Fig. 4). The amplitude of these waves is directly proportional to sympathetic activity.

After deep inspiration, a transient reflex vasoconstriction normally occurs (Fig. 4), and the magnitude of this response is also proportional to sympathetic activity. This reflex is obviously dependent upon intact sympathetic innervation and it disappears after lumbar sympathectomy.

Digital blood flow. The rate of flow of arterial blood into the distal extremity is studied by noting the change in digital volume after temporary venous occlusion. A manometrically controlled cuff is placed either at the base of a toe or at the ankle and suddenly inflated to a pressure of 50 millimeters of mercury to provide complete venous occlusion (Fig. 4). The upward shift of the baseline of the tracing, increasing digital volume, is the result of arterial inflow only. The increase in volume during a period of brief venous occlusion can be quantitatively expressed, but this measurement does not appear to be necessary in clinical application.

In most surgical candidates all the foregoing tests are applied and their results combined to provide a basis for planning therapy.

Selection of patients for grafting or endarterectomy. Ideal patients for arterial reconstructive procedures are those who can be shown to have segmental occlusions in the leg vessels with patent and normal or near-normal vessels distal to the localized obstruction. An obstruction, whether embolic or thrombotic, always increases the local pressure gradient, the magnitude of which is determined by the length of the obstruction and the amount of collateral flow around the occlusion. Winblad and coworkers, in studying pressures below an obstruction, found that a small gradient of pressure from below the obstruction to the foot indicates that the distal

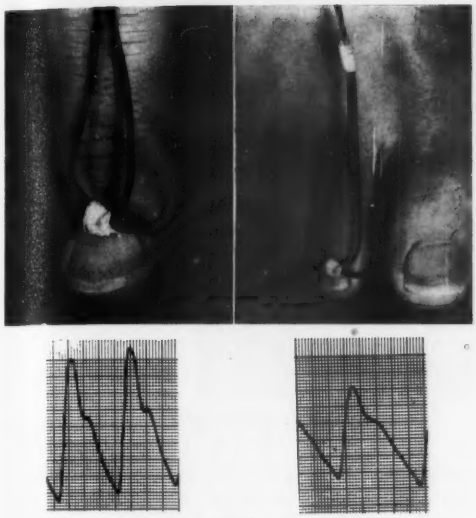

FIG. 2.

FIG. 2. Showing placement of the mercury strain gauge on the finger, left, and the toe, right, with the nonexpansile portion containing the lead connections over the base of the nail. The tracings shown represent typical normal digital pulses.

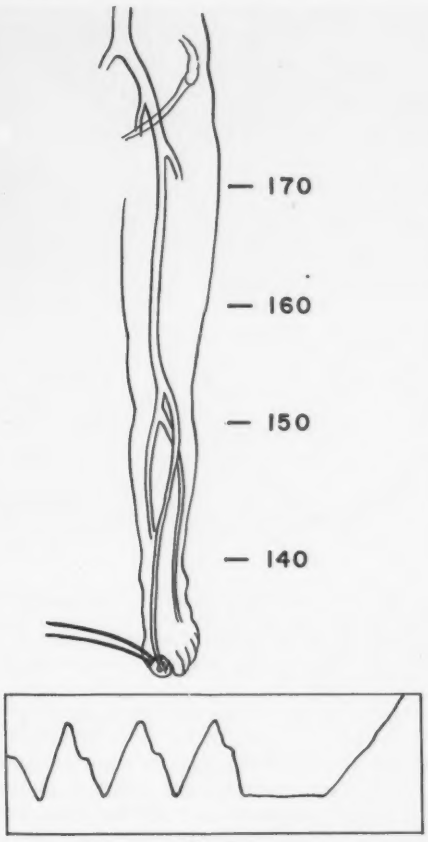

FIG. 3.

FIG. 3. This diagram shows typical normal systolic pressures at the levels at which they are determined as described in the text. A pneumatic cuff is placed at each level and inflated until the pulsations disappear, as shown in the tracing. The cuff is deflated until an upward shift in the baseline occurs, as noted in the tracing. The point at which the toe volume increases is the systolic pressure.

vessels are open and functional in at least a relative sense. Their determinations are made by direct arterial puncture, usually requiring a sizable operative procedure, whereas the studies herein described can be carried out with the plethysmograph both preoperatively and postoperatively without resorting to direct intra-arterial pressure recording. After successful placement of an arterial graft there is always an increase in the ankle pressure and digital pulse volume (Fig. 5).

The following case report illustrates typical preoperative findings in a patient with a single arterial occlusion.

CASE REPORT

A 69 year old man had a claudication in the left calf and a small ulceration over the head of the left first metatarsal, both present for about 6 months. The right leg was asymptomatic and had normal pulses. The only palpable pulse on the left was the femoral, which was slightly diminished. The pressure gradients and pulses are shown in Figure 6. A systolic pressure difference between the upper thighs of 65 millimeters of mercury indicated a narrowing of the left iliac artery. The large gradient of 80 millimeters of mercury from the left upper thigh to below the knee suggested that there was a long segmental occlusion of the superficial femoral artery, probably extending into the popliteal artery. Arteriography confirmed these findings. No reconstructive procedure or sympathectomy was advised and the patient eventually required a left above-the-knee amputation. Dissection of the vessels of the specimen confirmed the occlusions demonstrated by the plethysmographic study.

It has been possible to ascertain the accuracy of this screening method in 33 extremities by either arteriography or amputation, or both.

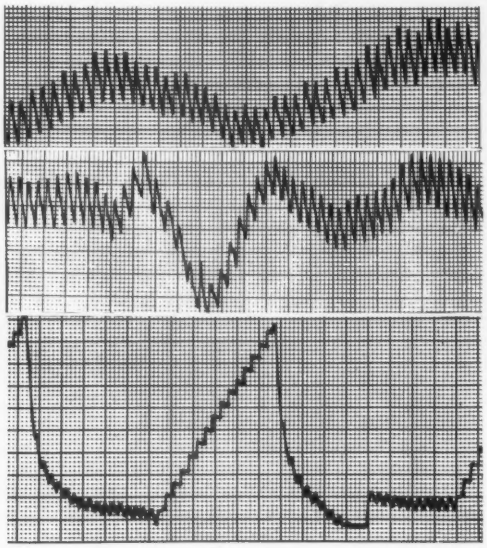

FIG. 4.

FIG. 4. The upper tracing shows the "slow waves" described in the text which are the result of rhythmic changes in vasomotor activity. The center tracing shows the sharp decrease in digit volume which is the result of vasoconstriction after a deep inspiration—the inspiratory reflex. The lower tracing shows a normal venous congestion test. The pneumatic cuff on the ankle is suddenly inflated to a pressure which is sufficient to stop venous outflow, producing the stepwise increase in digit volume. At the peak of the response the cuff is deflated and the digit volume rapidly returns to normal.

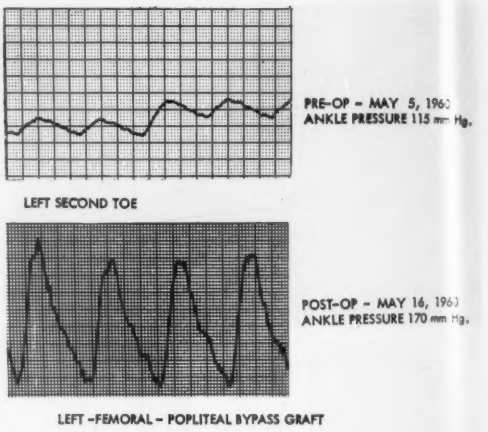
PRE-OP - MAY 5, 196
ANKLE PRESSURE 115 mm Hg.
LEFT SECOND TOE
POST-OP - MAY 16, 196
ANKLE PRESSURE 170 mm Hg.
LEFT -FEMORAL - POPLITEAL BYPASS GRAFT

FIG. 5.

FIG. 5. This figure illustrates the increase in digital pulse volume and ankle pressure when a bypass graft is functioning.

The site of occlusion was accurately localized in 28 of these extremities. In 3 of the 5 legs in which mistakes were made the primary site of occlusion was accurately predicted, but obstructions distal to this were predicted and did not exist. In 2 patients, inability to compress the arterial inflow resulted in inaccurate predictions.

Selection of patients for lumbar sympathectomy. Many patients are found not to have well localized occlusions and are, therefore, unsuitable for direct arterial surgery. In many of these patients, lumbar sympathectomy will be entertained as an alternative measure. Selection and evaluation of these patients constitute a complex and controversial problem. The success of sympathectomy appears to depend upon the arterial pressure head at any given level and upon the ability of the arteriolar bed at that level to respond to sympathetic denervation. This arteriolar reactivity is best tested by subjecting the extremity to a known vasodilatory stimulus and comparing the plethysmographic pulse volume response to the baseline control pattern. The dilating stimulus used is the reactive hyperemia test. A cuff is placed on the ankle and inflated to above systolic pressure and left in place for 5 minutes. It has been postulated by Wood and associates that during this period metabolites accumulate in the occluded area which have potent vasodilator activity. The cuff is deflated, and the immediate changes which occur in the pulse volume and the arterial inflow are studied.

Several factors are taken into consideration in selecting patients for sympathectomy.

1. Large pulse waves indicate good collateral circulation and the absence of significant disease of the small arteries, and patients with these findings generally have a good response to sympathectomy.

2. The presence of large slow waves and an active inspiratory reflex indicate responsive small arteries and arterioles, a combination giving a favorable response to sympathectomy (Fig. 4).

3. A significant increase in pulse volume and arterial inflow with an increase in pulse amplitude of at least 50 per cent, in response to the reactive hyperemia test, are probably the best indications that a sympathectomy will increase peripheral flow and lessen the symptoms of arterial insufficiency.

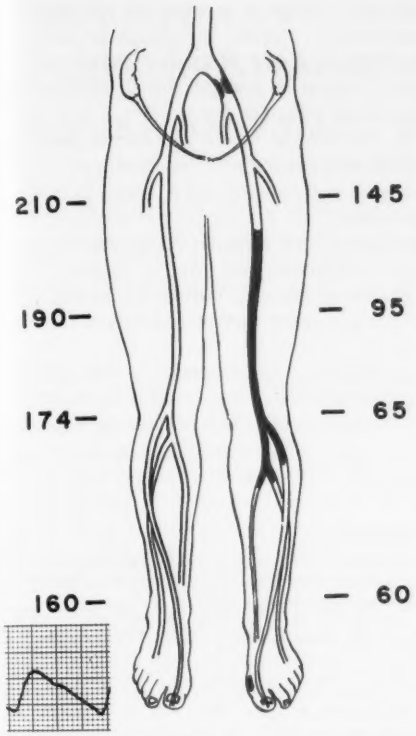

FIG. 6.

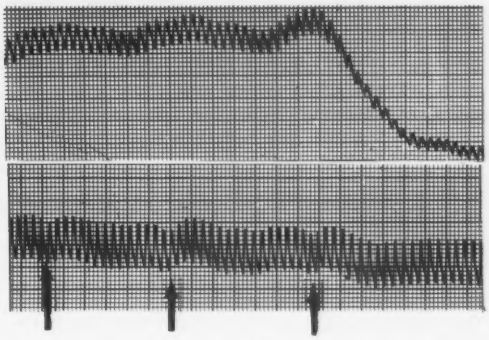

FIG. 7.

FIG. 6. This figure shows the pressures found in the patient described in the case report. The solid lines indicate the partial left iliac occlusion and the long obstruction of the femoral system. The pulse tracing on the right is essentially normal; there was no detectable pulse on the left.

FIG. 7. These two tracings from the same patient show some of the plethysmographic changes after lumbar sympathectomy. The upper tracing is preoperative, the lower postoperative. Note the increase in pulse volume and in the lower tracing that there is a decrease in the amplitude of the slow waves. The response to inspiration in the upper tracing was not elicited at the 3 points indicated by the arrows in the lower tracing, proving complete sympathetic denervation.

4. Absence of slow waves, lack of vasoconstrictive response to deep inspiration, and little or no change in pulse volume or arterial inflow with reactive hyperemia suggest that a poor response to sympathectomy should be expected.

At the present time 51 patients have been studied by these techniques. The correlation between the plethysmographic prediction of a good response to sympathectomy and the observed result will require longer follow-up periods. Based on the experience of Goetz and Smithwick, utilizing pneumoplethysmography, the correlation should be good and has been so to date.

DISCUSSION

In order to apply the information provided by plethysmography in evaluating patients with arteriosclerosis obliterans, the pathophysiology of arterial obstruction must be understood. When arterial occlusion occurs, the end pressure in the vessel is converted into lateral pressure which opens the collaterals and bypasses the occluded segment. Since the collateral vessels are of smaller caliber and the resistance to flow is increased, there is always a drop in the systolic pressure at the point of occlusion and beyond. The magnitude of the drop reflects the amount of resistance encountered and inversely the efficiency of the collateral flow. In anticipation of reconstructive surgery, it is vital that the state of the arterial bed distal to the occlusion be known. The determination of pressure gradients is again helpful. With patent arteries distal to an occlusion, collateral flow returns to the main arteries which can be considered lower resistance pathways. If the pressure gradients below an occlusion are normal, this is strong presumptive evidence that the distal arterial tree is patent. If distal obstruction is present the gradients are increased, indicating that the flow is through high resistance, small caliber collateral vessels.

The pulse contour and volume are also used as an indication of the amount of collateral

circulation. With short segmental occlusions and good collateral flow, the digital pulse volume may be normal. With poor collateral flow, the pulse wave loses its sharp systolic inflection and becomes flattened. With far advanced diffuse occlusive involvement, pulsatile digital flow may be completely absent.

In selecting patients for lumbar sympathectomy the problem is to determine whether a sustained decrease in the collateral and arteriolar resistance will occur. Since the greatest resistance to flow normally occurs in the arterioles, the response of this portion of the tree to a vasodilating stimulus gives an accurate estimate of the probable effect of sympathectomy. The reactive hyperemia test in our experience gives the most reliable results.

Complete sympathetic interruption abolishes the normal vasoconstrictive response to deep inspiration and the slow waves disappear (Fig. 7). These are absolute changes and failure completely to obliterate these responses to sympathetic discharge usually represents failure of complete interruption of the sympathetic trunk.

Combining preoperative evaluation, arteriography, and operative monitoring, our early graft failure rate has been reduced from 30 per cent to 6 per cent. Another advantage of this technique is that the same objective tests can be utilized in the immediate and late postoperative periods in determining the response to operation. Follow-up arteriography is no longer utilized to determine the success of reconstructive surgery as this is easily accomplished by plethysmographic techniques.

SUMMARY

A new simple mercury strain gauge plethysmograph has been described which has proved extremely valuable in selecting patients for reconstructive surgery or sympathectomy. The simplicity and ease of application of the instrument permits its routine use in evaluating patients with vascular disease.

In the clinical use of this instrument the following information may be obtained: (1) the extent and location of main vessel occlusive involvement; (2) the functional adequacy of the distal arterial tree when reconstructive surgery is contemplated; and (3) the degree to which sympathectomy will reduce collateral and arteriolar resistance and increase blood flow to the limb.

In addition to preoperative evaluation, the strain gauge plethysmograph permits operative monitoring in selected cases and provides a critical method of determining the late results of reconstructive vascular surgery.

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AN IMPROVED GUSSET FOR THE RELIEF OF INFUNDIBULAR STENOSIS IN SURGICAL CORRECTION OF TETRALOGY OF FALLOT DEFECTS

HUGH E. WILSON, M.D., F.A.C.S., EUGENE N. NOMICOS, M.D.,
RICHARD W. ERNST, M.D., WILLIAM M. ASHE, M.D.,
JOHN L. KEE, JR., M.D., F.A.C.S., and P. O'B. MONTGOMERY, M.D., Dallas, Texas

THE COMPLETE CORRECTION of the tetralogy of Fallot lesions by open heart methods has with experience yielded a satisfactory mortality of 12.5 per cent in our hands during the past 2 years and has become the operation of choice for the majority of these lesions. One of the most important technical aspects of this repair is adequate relief of the right ventricular outflow tract obstruction whether it be purely infundibular and valvular, or infundibular and valvular with a hypoplastic pulmonary artery. This has been documented by Kirklin and co-workers.

The use of compressed ivalon, polyvinyl alcohol sponge, as a "roof" or "reconstruction" to relieve obstruction of the right ventricular outflow tract has been described by Lillehei, McGoon, and Kirklin and their associates. However, the use of this substance presents several problems. First, if the sponge is sufficiently compressed to prevent severe bleeding through its interstices after insertion in the heparinized patient, it is leathery in consistency, difficult to suture delicately, and retards the ingrowth of granulation tissue and fibroblasts. Thus, it acts as a foreign body which does not become a part of the surrounding tissue. It may act as a nidus for serious infection. Second, if the ivalon compression ratio is low enough to allow the ready ingrowth of granulation tissue and fibroblasts, it is a harrowing and time-consuming procedure to stop the bleeding through its interstices. In the past, on clinical cases we have spent as long as 45 minutes applying topical thrombin and gelfoam to effect hemostasis. Third, compressed ivalon used as a gusset in the outflow tract of the right ventricle, if not greatly compressed, presents a roughened surface which at least in the experimental animal may result in thrombus formation on the inner surface of the gusset.[1]

Gross has used pericardium alone in the relief of outflow tract obstruction in open heart correction of the tetralogy lesions. This has avoided some of the problems cited, but the experience of Bailey and Lepley and their associates, demonstrating marked shrinkage, degeneration, necrosis, and tissue reaction when pericardium is used within or about the chambers of the heart, has led us to avoid using it by itself in this situation.

In a search for a solution to these problems a combination of an autograft of pericardium and slightly compressed ivalon sponge, experimentally and clinically, has seemed to eliminate the objections to both of these substances used individually.

METHOD

Prior to opening the pericardium its anterior surface is stripped of all pericardial fat and areolar tissue. A large ellipse is excised. After digital intracardiac exploration of the outflow tract, an ellipse of ivalon sponge compressed approximately 3 to 1 and slightly thicker at one apex is fashioned to a dimension which will adequately relieve any obstruction of the outflow tract not relieved by resection of the crista supraventricularis. The pericardium is then sutured to the ivalon with its smooth surface away from the plastic. A continuous suture of No. 5–0 atraumatic vascular silk is used, taking

From the Division of Cardiac and Thoracic Surgery and Department of Pathology, The University of Texas Southwestern Medical School, Dallas.

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[1]Gusset: A triangular or tapered piece of material let into a garment to strengthen or enlarge some part, to afford ease in movement.—New English Dictionary on Historical Principles, J.A.H. Murray, vol. 4, p. 145, Oxford University Press, 1901.

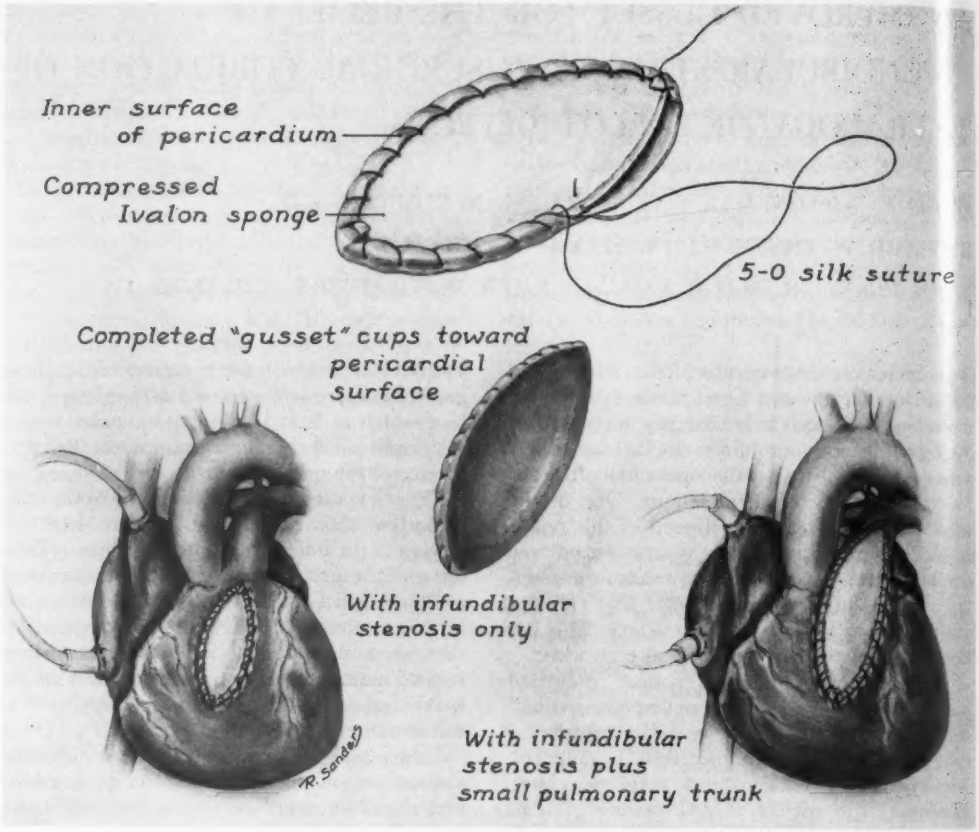
Inner surface of pericardium
Compressed Ivalon sponge
5-0 silk suture
Completed "gusset" cups toward pericardial surface
With infundibular stenosis only
With infundibular stenosis plus small pulmonary trunk
R. Sanders

FIG. 1. The gusset is prepared by suturing an autograft of pericardium to the inner surface of the 3 to 1 compressed ivalon ellipse. No. 5–0 vascular silk sutures are used, taking care to suture only through the outer edge and surface of the ivalon. Slight tension is kept on the pericardium to make its inner surface concave. The gusset may be fashioned to relieve outflow tract obstruction alone, as on the lower left, or obstruction due to infundibular stenosis and a hypoplastic pulmonary artery, as on the lower right. The gusset is sutured into the right ventriculotomy or right ventriculotomy and pulmonary arteriotomy with continuous sutures of atraumatic No. 3–0 silk.

care to place the sutures only through what will be the outer surface and edge of the completed gusset. If slight tension is kept on the pericardium during this suturing, the gusset will be concave on its inner surface (Fig. 1). The outer convexity of the gusset is maintained in situ.

After the establishment of total cardiopulmonary bypass, excision of any resectable infundibulum, and closure of the ventricular septal defect, the gusset is sutured into the right ventriculotomy or right ventriculotomy and pulmonary arteriotomy (Fig. 1) with continuous sutures of No. 3–0 atraumatic silk. In some clinical cases the ventriculotomy has been sutured and inadequate relief of outflow tract obstruction demonstrated by direct pressures taken with the Harken intracardiac cannula. In these cases the ventriculotomy has been reopened and the gusset sutured into place.

EXPERIMENTAL WORK

Anesthetized mongrels weighing from 15 to 25 kilograms were subjected to thoracotomy and total cardiopulmonary bypass. Gussets as illustrated in Figure 1, composed of ivalon

sponge compressed 3 to 1 and lined with autografts of pericardium, were inserted into a right ventriculotomy or a right ventriculotomy and pulmonary arteriotomy. Ten of these dogs were sacrificed at intervals of 10 days to 6 months. In the early experiments no attempts to avoid infection were made. Later in the series the ivalon was soaked in a penicillin-streptomycin solution prior to insertion in the heart and the dogs were given prophylactic antibiotics for 5 days postoperatively. After sacrifice the hearts of all animals were examined grossly in the fresh state and fixed and sectioned for microscopic examination.

These experiments and gross and microscopic examinations allowed the following conclusions: (1) With gussets constructed as described there is no problem of bleeding through the ivalon after insertion. (2) The pericardial surface of the gusset should be sutured flush with the right ventricular endocardium to avoid thrombus formation on the cut myocardial edge. (3) There had been significant growth of rich vascular granulation tissue into the ivalon sponge interstices from the myocardium and from the adhesions on the outside of the gusset as well as from the pericardial, inner, surface at 10 days. There is beginning autolysis of the pericardial lining of the graft at this time, but a smooth inner surface is maintained. (4) By 2 months the granulation tissue within the ivalon had become more mature and the pericardium had become hyalinized. (5) At 3 months the granulation tissue within the ivalon had become fibrous and had completely invaded the ivalon. The pericardium had been replaced by smooth fibrous tissue. The endocardium extended intact over this thin layer of connective tissue, giving a glistening lining. (6) In the experimental animal, after 4 months, there may be formation of mature cartilage and bone in the fibrous lining of the gusset under the endocardial layer. (7) In some of the early animals in which no aseptic technique or precautions against infection had been used, small microabscesses occurred within the ivalon. These were well localized and surrounded by budding granulation tissue. They were well contained, with no tendency to empyema, gusset sequestration, or infection.

DISCUSSION

Gussets composed of ivalon compressed approximately 3 to 1 and lined with pericardium as described have been used in 16 patients. Two of these patients expired within 2 days of surgery, allowing postmortem examination of the heart. In both of these cases the concavity of the gusset was maintained and there was no thrombus on either its smooth inner lining or at the junction of the gusset with the right ventricular endocardium. In clinical use of this technique there has been only one opportunity to examine the gusset after a prolonged period. This examination was in an 11½ year old boy who was reexplored 6 months after his initial operation because of multiple small atrial septal defects missed at the time of correction of the tetralogy lesions. With relief of the resistance to pulmonary artery flow the left to right shunt at the atrial level had increased, causing marked dilatation of the right side of the heart. In this patient the ventricle was reopened beside the gusset at the second operation to rule out a persistent leak at the ventricular level. This incision allowed careful inspection of the gusset. It had shrunk little in size and was lined with a thin, smooth, glistening membrane which was continous with the endocardium elsewhere in the right ventricle. It had maintained its inner concave surface. The circumference of the outflow tract to the right ventricle was more than adequate. In this patient the gusset had been extended beyond the bifurcation of the pulmonary artery because of an extremely small main pulmonary artery trunk. The smooth lining and proper configuration were continous throughout.

In none of these patients has there been a problem with bleeding through the gusset or ventriculotomy at the time of operation. Not all patients undergoing corrective surgery for cyanotic tetralogy of Fallot at this clinic have required the use of the gusset. However, we do not hesitate to use it at this time if there is any question of significant residual gradient, because of the simplicity of the technique. It has also been used in 3 patients with isolated pulmonic stenosis in whom opening the valve in three rudimentary commissures beyond the annulus has left a residual gradient, as measured on the operating table, of over 100 millimeters of mercury.

SUMMARY

A method has been devised to relieve the outflow tract obstruction in complete surgical

correction of the tetralogy of Fallot when resection of the infundibulum is not sufficient. A gusset composed of ivalon compressed 3 to 1 and lined with pericardium is used. This method avoids the disadvantage of ivalon alone because the ivalon does not require marked compression and, therefore, allows the rapid growth of vascular granulation tissue into the prosthesis while providing excellent hemostasis, a concave configuration to the prosthesis, and a smooth inner surface which it has been found will not propagate thrombus.

The technique has been tested in animals and successfully utilized in 16 patients without complications considered to be caused by the gusset.

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RECONSTRUCTION OF A FUNCTIONING VAGINA FOLLOWING RADIATION THERAPY FOR CANCER OF CERVIX

RAYMOND J. SIMMONS, M.D., F.A.C.S., and D. RALPH MILLARD, JR., M.D., F.A.C.S.,
Miami, Florida

THE MOST WIDELY USED THERAPY for cancer of the cervix in this country is radiation, delivered through external ports, and by direct application of radium or radioactive cobalt to the cervix. This treatment usually results in a variable degree of narrowing and rigidity of the upper portion of the vagina which may interfere with intercourse. Occasionally, obliteration of the upper one-half to three-fourths of the vaginal canal results from the irradiation and, thus, renders intercourse impossible.

Since cancer of the cervix occurs chiefly in relatively young, sexually active women, a radiation vaginitis with partial obliteration becomes a distressing disadvantage of this form of therapy. In addition, a high percentage of patients with early cancer of the cervix are cured by radiation therapy and, as a consequence, may look forward to a normal life expectancy. In fact, Moss reports 5 years survival in 70 per cent of patients with stage 1 carcinomas of the cervix and in 48 per cent with stage 2 carcinomas. Thus, both the youth of these patients and their excellent prognosis increase the importance of the unsatisfactory side effect of partial or total sexual incapacity. Reconstruction of a functioning vagina after partial obliteration by irradiation requires, first, dissection of a new pocket and, second, lining and maintenance of this cavity.

DEVELOPMENT OF A NEW VAGINAL POCKET

An incision is made in the posterior vaginal wall, well below the obliterated upper vagina. A space is then created by sharp and blunt dissection between the obliterated vagina and the rectum, extending up beneath the posterior cul-de-sac. The irradiated cervix and upper vagina are avoided in the dissection for the following reasons: (1) the theoretic possibility of disturbing quiescent tumor cells and (2) the impaired blood supply in the irradiated tissue. The peritoneum is identified and after careful mobilization is pushed upward from the rectum and bladder. A surprisingly bloodless plane of dissection, measuring about 10 centimeters in length and 5 centimeters in width, is readily established.

TECHNIQUE OF LINING THE CAVITY

By this method of dissection, massive scarring from the radium is avoided and the pocket developed has been found to have an adequate blood supply in its walls to receive and hold a split skin graft. It is vital not only to line the pocket with skin and prevent the walls from sticking but also to maintain the space of the cavity and counteract contracture. Insertion of a mold bearing a skin graft into the dissected pocket will line and dilate the cavity until it is able to maintain itself. Abbe in 1898 was the first to report on the application of skin grafts to the vagina in the case of congenital absence. Subsequently, inlay grafting of the vagina has been elaborated by McIndoe in 1937, Owens in 1942, and Adams in 1943.

Once a pocket of maximum depth has been dissected, the fitting of a mold is the next step toward reconstruction. The mold to carry the skin graft has a phallic shape but, of course, must vary in size according to the patient and the potential vagina. The simplicity of shaping a mold of dental compound or gutta-percha to fit the individual pocket at the time of operation has merit. Warm wet compresses packed into the newly created pocket hasten hemostasis while a graft is being cut. With the patient already in lithotomy position, a hairless area of the buttocks or thigh is available and has been prepared. A medium split graft is taken freehand in one piece or by the electric dermatome. The mold is painted with collodion or mastisol, and the graft is draped over its end with the raw surface out. The excess skin is trimmed along

one or both sides, and any seams are stitched with continuous No. 6-0 chromic catgut to give a fit like the finger of a glove. The skin covered mold then is inserted deep into the vaginal pocket and held in position by suturing the labia over it. A Foley catheter placed in the bladder at the time of operation is retained 1 week postoperatively.

Hemostasis and immobilization must be meticulous because it is extremely important that the raw surface of the graft lie in direct contact with the raw vaginal pocket. This condition must be maintained for at least 1 week to insure that the graft develop a new blood supply from its recipient bed. By this time the graft will have become adherent enough so that the mold can be removed safely, cleaned, and reinserted. If there has been a small area of skin loss, complete epithelization will follow within several weeks. A large loss necessitates the insertion of an adequate patch graft on the mold to speed up the epithelial coverage of this pocket and to reduce the potential contracture.

POSTOPERATIVE FOLLOW-UP

The mold is maintained for 7 days, after which time it is removed for short intervals allowing it to be cleaned and the pocket to be irrigated. This regimen is continued for another 3 weeks. The patient then is urged to return to the natural dilation of sexual intercourse but is encouraged to wear the mold during sleeping hours for several months.

The skin graft taken from the buttocks or thigh soon takes on the appearance and general texture of mucous membrane. It was first reported by Pierce and associates that thigh flaps inturned for vaginal lining had the gross and microscopic appearance of vaginal mucosa after 20 years, and a similar phenomenon occurs with split grafts.

SUMMARY

A simple method of dissection and inlay grafting is described for reconstructing a functional vagina after radiation obliteration of the vagina secondary to the successful treatment of cancer of the cervix.

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A MODIFIED PROCEDURE FOR COMPLETE REPAIR OF TOTAL ANOMALOUS PULMONARY VENOUS DRAINAGE

HARRIS B SHUMACKER, JR., M.D., F.A.C.S., and HAROLD KING, M.D., F.A.C.S.,
Indianapolis, Indiana

THE SURGICAL CORRECTION of partial transposition of pulmonary venous return associated with an atrial septal defect presents no particular difficulty. Some forms of total anomalous pulmonary venous drainage also can be corrected by relatively simple surgical maneuvers, particularly those in which the pulmonary veins enter the right atrium directly or through a pouch and those in which they enter the right atrium through the coronary sinus. Correction of the most common abnormality associated with total anomalous pulmonary drainage has proved a greater challenge. In this situation, the right and left pulmonary veins enter a common posterior venous trunk which continues as a persistent left superior vena cava and enters the right superior vena cava via the innominate vein. The original closed, partially corrective procedures provided considerable palliation. They were, however, attended with difficulty in effecting a wide communication between the left atrium and the posterior pulmonary venous trunk or the left pulmonary veins, especially in very small infants. Furthermore, judging from reports in the literature, there was a relatively high mortality and in no case that we are aware of was it possible to ligate or divide, or even substantially constrict, the left superior vena cava with survival of the patient. It was, therefore, a great step forward when Cooley and Ochsner described an interatrial method for complete correction. This entailed an open operation with total cardiopulmonary bypass and extracorporeal circulation. The right atrium was opened and the left atrial cavity was exposed by an incision through the atrial septum. An incision was then made through the posterior left atrial wall and through the presenting surface of the posterior venous trunk. The two were anastomosed together and the atrial septum was reconstructed so as to close the patent foramen ovale or the atrial septal defect and to shift the septum in such a fashion as to increase the size of the left atrial cavity. In this report a modification of this method is described which we believe advantageous. It was suggested some time ago during the course of an operation upon a 3 month old infant in whom the small size of the heart proved a handicap in carrying out the procedure through the interatrial approach.

The operation is performed with total cardiopulmonary bypass and extracorporeal circulation. An arterial inflow cannula is introduced into one common femoral artery and the venous outflow catheters into the inferior and right superior venae cavae via the right atrium. The left superior vena cava is surrounded with a tape so that it can be occluded once bypass is begun. An adequate incision is made through the right atrial wall longitudinally and rather close to the left side (Fig. 1). The atrial cavity is inspected and either the atrial septum is excised or opened widely through a curved incision along its right lateral attachment. In all of our patients the right pulmonary veins have joined the common posterior venous trunk to the right of the heart itself. A horizontal incision is then made into the pulmonary venous trunk to the right of the heart and is extended across the interatrial groove into the right atrial wall. It is then extended through both the posterior left atrial wall and the posterior venous trunk as far as is possible. Working more or less outside of the heart rather than within the atrial cavity one is able to suture the posterior venous trunk to the posterior wall of the left atrium without difficulty. The suture is begun at the left ends of the two incisions. The anastomosis can be made larger than would be possible through the atrium itself by continuing the line of suture beyond the left atrial wall across the interatrial groove and bringing the

From the Department of Surgery, Indiana University School of Medicine, Indianapolis, Indiana. This work was aided by grants from the Indiana Heart Foundation, James Whitcomb Riley Memorial Association, and PHS research grant H-2035 (C-5) from the National Heart Institute, National Institutes of Health, Public Health Service.

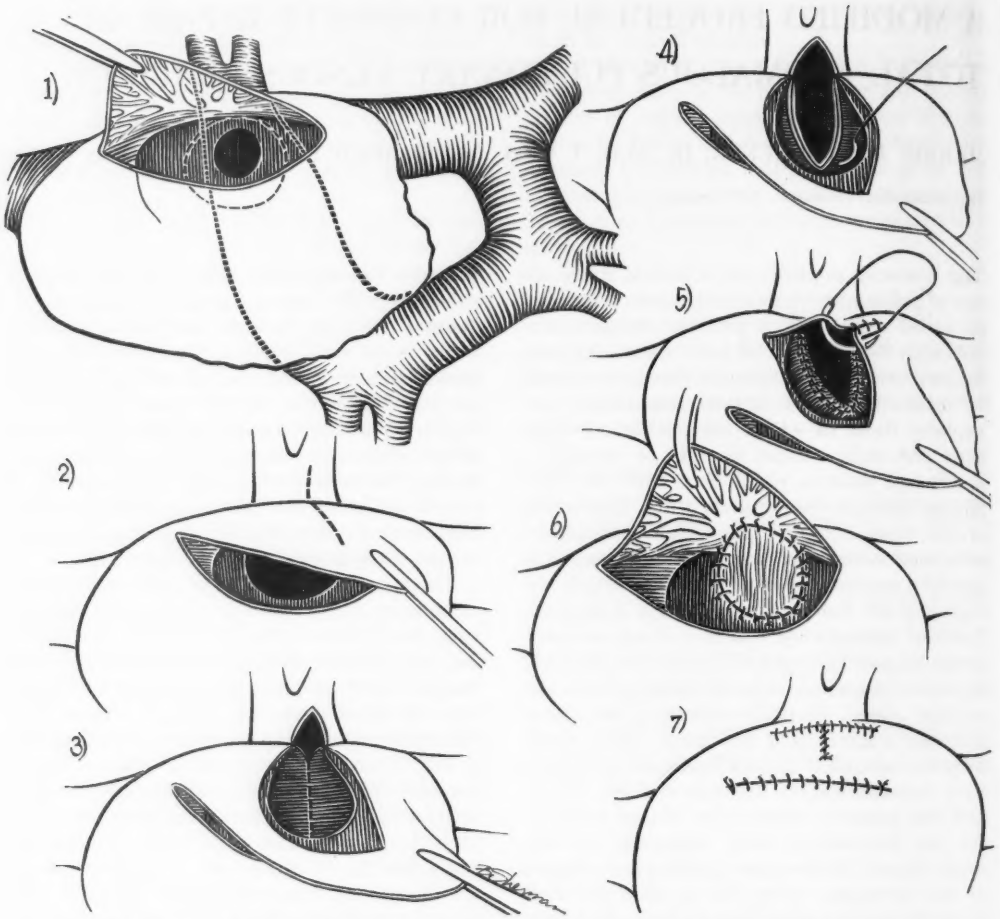

FIG. 1. Drawing illustrating operative technique: *1*, The longitudinal right atrial incision is made and the atrial septum excised. In some cases, instead, the atrial septum is opened widely by means of a curved incision with its convexity toward the right. *2*, The incision is made from the pulmonary vein across the interatrial groove and into the right atrial wall. *3*, It is extended through the left atrial wall and the posterior venous trunk. *4*, The incisions in the posterior left atrial wall and venous trunk are sutured so as to effect a wide communication between them. *5*, The lateral part of the horizontal right atrial incision is sutured to the remaining portion of the incision in the pulmonary vein. *6*, The atrial septum is reconstructed so as to close the defect and shift it anteriorly. In some cases this is effected by use of an atrial flap but generally by means of a patch graft. *7*, The remaining right atrial incisions are closed.

right end of the right atrial incision together with the remaining incision in the pulmonary vein. The residual portion of the horizontal right atrial incision is then closed. The atrial septum is repaired through the original right atrial incision by using either the atrial septal flap or a plastic circular graft. This is done in such a manner as to close the atrial septal defect and to shift the atrial septum anteriorly in order to enlarge the left atrial cavity. The original vertical atrial incision is repaired and the left superior vena cava ligated.

We have had an opportunity to apply this modified operation in 6 instances. It was tech-

nically easy in all. Four of the patients made uneventful recoveries. Their ages at the time of operation were 3½, 12, 17, and 11 years. The first 3 patients had had previous partial corrective procedures, the first, 3, the second, 2, and the third, 7 years, beforehand. The 3½ year old child was in particular difficulty prior to operative treatment, in chronic failure with a huge heart, marked hepatomegaly and frequent episodes of severe pulmonary edema. Each made an uncomplicated recovery and has done well since discharge.

Though the operative correction was technically easy in 2 tiny 3 month old infants, neither survived. Early in both marked and persistent cardiac failure developed with ascites and edema. The failure had persisted and indeed progressed in spite of hospitalization and intensive medical management.

It is our opinion that the modification suggested makes the complete correction of total anomalous pulmonary venous drainage technically easier than the original method and permits an anastomosis of maximal size.

SUMMARY

A modification of Cooley's method for correction of total anomalous pulmonary venous return is described. It has the advantages of permitting one to accomplish the left atrial-pulmonary venous trunk anastomosis more or less from outside the heart rather than from within the atrium and of making possible an anastomosis of maximal size.

REFERENCES

1. COOLEY, D. A., and OCHSNER, A., JR. Correction of total anomalous pulmonary venous drainage. Surgery, 1957, 42: 1014.

THE SURGEON'S LIBRARY

Reviews of New Books

THE EXCELLENT SYMPOSIUM *Peptic Ulceration*[1] by Wells and Kyle also contains chapters written by six other contributors. The authors have presented in some detail much of the recently acquired knowledge concerning peptic ulceration. The content of the book is well organized and the important aspects of the problem of peptic ulcer are covered. Each author has made use of a rather complete bibliography listed at the end of each chapter.

The section on histopathogenesis of chronic peptic ulceration by Sircus provides an excellent critical estimate of this problem. The need for further advances in the knowledge of the various mechanisms responsible for peptic ulcer is stressed. The principles of the surgical treatment of peptic ulcer are thoroughly discussed by the authors in terms of the concept that peptic ulcer is due to the aggressive action of gastric juices and to local pathologic changes. Surgical procedures are not described in great detail, except for those techniques that may be utilized in dealing with the unexpected and difficult situations encountered by the surgeon. The management of the difficult duodenal stump after gastric resection is excellently presented. The chapters by Welbourn dealing with the delayed complications of gastric resection have been prepared exceptionally well and many of his own observations and work in connection with his studies on postgastrectomy syndromes are represented.

I sympathize with Welbourn in his difficulty in determining accurate data as to the incidence of recurrent ulcer. His plea for more accurate methods and standardization of reporting follow-up data in order to evaluate the results of the main surgical procedures is more than justified.

The value of this book has been increased by the translation into English of the leading German classical contributions to gastric surgery.

This symposium can be recommended not only to surgeons but also to all physicians and students who are interested in the problem of chronic peptic ulcer and gastrointestinal physiology. The authors have accomplished in concise form what they had set out to do.

—Harry A. Oberhelman, Jr.

AN EXCELLENT, concise presentation of present information and trends in the field of reproduction has been made in the publication *Survey of Research in Gestation and the Developmental Sciences*.[2]

By design, the individual sections are quite superficial which is overcome by the accompaning bibliography which makes this book a valuable aid to those who wish more detailed information, as well as for those who do or contemplate research in this area. The choice of topics emphasized is most timely; for example, the chapters on the placenta and the immunologic aspects of pregnancy are most informative.

A unique feature of the final chapter is the list of general information sources in the fields of reproduction, endocrinology, and physiology and anatomy. These references, as well as the entire book, would be most useful to those who desire background knowledge on the subject of reproduction. This book is recommended to prospective students as well as researchers, teachers, and practitioners interested in this study.

—Albert B. Gerbie.

THE AUTHORS of the book *Surgical Disease of the Pancreas*[3] have drawn from a large personal experience to review all aspects of this particular disease exclusive of diabetes. Allen O. Whipple has included a fine résumé of this history of pancreatic disease. The experiences of a number of recognized authorities who are interested in specific subjects, such as anatomy and embryology, physiology, laboratory diagnosis, meconium ileus, and islet cell and ulcerogenic tumors of the pancreas have been related.

The chapters on pancreatitis which include pancreatic trauma, etiologic considerations in pancreatitis, physiologic changes, diagnosis, treatment, and prognosis were written by the senior author. He has emphasized the importance of understanding the natural history of pancreatitis and has separated pancreatic inflammatory disease into the following: that associated with gallstones, that resulting from alcoholism, and that due to other causes, such as postoperative pancreatitis as well as the unusual forms infrequently encountered. He has also emphasized that only through an understanding of the origin of the disease can there be effective adequate treatment. When pancreatitis is associated with gallstones, he points out that in a

[1] PEPTIC ULCERATION. By Charles Wells and James Kyle, M.B., M.Ch., F.R.C.S., F.R.C.S.(I). Foreword by Lester R. Dragstedt. 260 pages, 41 illustrations. $8.75. Edinburgh and London: E. & S. Livingstone, Ltd., 1960. Baltimore: The Williams & Wilkins Co., Exclusive U. S. agents.

[2] SURVEY OF RESEARCH IN GESTATION AND THE DEVELOPMENTAL SCIENCES. By Jack Davies, M.A., B.Sc., M.D. 203 pages. $6.00. Baltimore: The Williams & Wilkins Co., 1960.

[3] SURGICAL DISEASES OF THE PANCREAS. By John M. Howard, M.D., F.A.C.S., and George L. Jordan, Jr., M.D., M.S., F.A.C.S. 607 pages, 197 illustrations. $20.00. Philadelphia and Montreal: J. B. Lippincott Co., 1960.

majority of these cases improvement occurred after surgical correction of the biliary tract disease. In alcoholic pancreatitis, which includes most instances of pancreatic calcification, no form of surgical treatment has been uniformly effective. Sphincterotomy, choledochoduodenostomy, and distal pancreatectomy with pancreatojejeunostomy have been performed by the authors without great success. Recent efforts have been directed toward resection of the pancreas in the alcoholic group and in a limited number of cases the results have been encouraging.

Chapters on pancreatic cysts, tumors of the pancreas and periampullary area, pancreatic resection, and pancreatic fistulas were written by Jordan, and each of these subjects has been analyzed most effectively.

This book is beautifully illustrated and replete with simple, concise tables. The volume is devoted almost entirely to a clarification of the clinical aspects of pancreatic disease. Only a minimal amount of experimental data have been included.

This book will provide an excellent source of direct as well as reference information for anyone interested in pancreatic disease. —*Marion C. Anderson.*

THE STORY about the introduction of rubber gloves into the operating room by Halsted to protect the hands of his beautiful chief operating room nurse, whom he later married, appealed to me greatly as a medical student, and I have enjoyed passing it on each year to my students. The author has spoiled this story in *The Surgeon's Glove*,[4] to some extent, by demonstrating that priority should certainly be accorded to others and has even raised substantial doubts about the romantic aspects of the Halsted story.

In this charming volume, the origins of the use of gloves during surgery are painstakingly traced. The theme of the book is that "a good idea can be too simple. It could be brought up again and again, only to be overlooked because it lacks the enticement of mystery or the charm of complexity." The author is fascinated by the fact that Halsted, and many other famous surgeons before him, somehow failed to recognize the significance of the wearing of rubber gloves for purposes of asepsis. Many interesting details are presented concerning antiseptic surgery and the gradual evolution to aseptic surgery as well as the fact that many outstanding surgeons who professed to practice aseptic surgery during the first decade of this century actually had an incomplete understanding of all that it should encompass.

This little book is written in a clear and simple style. The reader is given the opportunity to discover, along with the author, gaps in knowledge which were common during the years when aseptic surgery gradually gained acceptance.

Practicing surgeons, residents and medical students, and, indeed, anyone interested in surgery would be delighted with this volume. Some of the most important experiments which proved the superiority of aseptic over antiseptic techniques are recounted vividly, and there are few of us who would not benefit by reviewing this evidence which is so charmingly presented. Certain details, such as experiments demonstrating the ineffectiveness of alcohol as an antiseptic agent, are perhaps not sufficiently emphasized in modern surgical practice. —*Charles Kirby.*

A VERY GOOD REVIEW of present day opinions in regard to portal hypertension and the surgical complications, viewed through the eyes of a surgeon, are presented in a most acceptable form in *The Surgical Treatment of Portal Hypertension, Bleeding Esophageal Varices, and Ascites*.[5] In addition, a good historical review is given of the various procedures which have been recommended in the past. The material presented with regard to what the majority now considers to be the treatment of choice for bleeding esophageal varices with or without ascites as well as the treatment of ascites alone makes this volume timely.

Unfortunately, the final solution to this problem has not been attained, and it is my opinion that the author, like most surgeons, prefers a direct portacaval shunt between the portal vein and the inferior vena cava in preference to a splenorenal shunt. As evidence of this, a much more extensive series of illustrations is presented to depict the former as compared to the latter. From personal experience, there seems to be some question as to whether the portacaval shunt is better since it, unfortunately, seems to result in more postshunt neuronutritional disturbances than does the splenorenal shunt.

The book is unique in that it gives the personal opinion of many other surgeons in this field on the various aspects of this condition. A reading of these views clearly demonstrates that there is a lack of uniformity in the opinions of these authorities, indicative of course, that the final solution has not been attained for the treatment of cirrhosis of the liver and its complications.

For the student interested in this subject it will be difficult to find a more complete bibliography than that which is presented in the volume since there are 250 pages and 96 of these list the bibliography.
—*Robert R. Linton.*

THE COMBINED EFFORTS of the staff of the Queen Charlotte's Maternity Hospital, London, went into the preparation of the text the *Queen Charlotte's Textbook of Obstetrics*.[6] This is a 120 bed institution with antenatal and postnatal clinics. In 1955, there were 3,105 in-patient deliveries and 468 supervised home deliveries. It has been designated as a teaching hospital by the National Health Service.

The textbook itself is a 524 page book printed in large, clear type on heavy paper complete with many charts, illustrations, and photographs, both gross and microscopic. It is currently in its tenth edition.

The material contained within the text is aimed primarily at undergraduate medical students and mid-

[4] THE SURGEON'S GLOVE. By Justine Randers-Pehrson, M.A. 95 pages, 11 illustrations. $4.50. Springfield, Ill.: Charles C Thomas, 1960.

[5] THE SURGICAL TREATMENT OF PORTAL HYPERTENSION, BLEEDING ESOPHAGEAL VARICES, AND ASCITES. By M. Judson Mackby, M.D. 223 pages, 49 illustrations. $10.50. Springfield, Ill.: Charles C Thomas, 1960.

[6] QUEEN CHARLOTTE'S TEXTBOOK OF OBSTETRICS. By Members of the Clinical Staff of the Queen Charlotte's Maternity Hospital, London. 10th ed. 524 pages, 240 illustrations. 50s. net. London: J. & A. Churchill Ltd., 1960.

wives, as there is little theorizing or detail and no bibliography. Rather, it is a commentary on all phases of obstetrics from conception through delivery and the puerperium as practiced at that hospital. For the more advanced student or teacher, especially in this country, its chief value would seem to be in comparing views on the many subjects discussed.

Of particular interest to this latter group would be the differences in terminology which crop up frequently in the literature and, undoubtedly, cause certain confusion. By reading about these subjects in a text, a better understanding of them would be achieved. Some examples of these differences in terminology are found in the use of the phrase "carneous mole" as a synonym for "missed abortion," the word "over lapping" as we use "overriding," and the term "pelvic grips" in describing abdominal palpation of the pregnant woman at term.

Frequently, striking differences occur in the practices urged in this book as compared to the views of many obstetricians in this country. They, for example, do not advocate the use of episiotomy or forceps except under very strict indication, nor do they recognize particular need for repeat cesarean section. Such views are held also by many here, while others are absolutely opposed. The reference to the muscle in the cervix and the relative disregard of afibrinoginemia are other points which are open to dispute.

Excellent sections on the placenta, on "domiciliary obstetrics," and on the baby, as well as complete coverage of the physiology of pregnancy and labor, the mechanisms and management of labor, and the total care of the mother, all go to make this a very useful basic textbook of obstetrics. As any book which represents the views of only one institution, this volume will find its major acceptance in that particular area, but might well be interesting and useful to everyone interested in obstetrics. —*J. W. Roddick, Jr.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

PROSTHETIC VALVES FOR CARDIAC SURGERY. Edited by K. Alvin Merendino, M.D. 586 pages, 383 illustrations. $8.25. Springfield, Ill.: Charles C Thomas, 1961.

CANCER; THE SIGNIFICANCE OF DELAY. By Robert Sutherland, M.D., D.P.H. 206 pages, no illustrations. $6.00. London: Butterworth & Co., 1961.

A STEREOSCOPIC ATLAS OF HUMAN ANATOMY. SECTION V —THE ABDOMEN. By David L. Bassett, M.D. Slides 133–152. $16.50. Portland, Ore.: Sawyer's Inc., 1961.

SURGERY OF ACUTE ABDOMEN. By John A. Sheperd, M.D., F.R.C.S.(Ed.), F.R.C.S.(Eng.). 1210 pages, 43 illustrations. $18.50. Baltimore: The Williams & Wilkins Co., 1961.

ADVANCES IN BLOOD GROUPING. By Alexander S. Wiener, M.D., F.A.C.P. 539 pages, illustrated. $11.00. New York: Grune & Stratton, Inc., 1961.

DIE INTERSEXUALITAET. By Prof. Dr. Claus Overzier. 538 pages, 193 illustrations. $28.35. Stuttgart: Georg Thieme Verlag, 1961.

GYNAEKOLOGISCHE UROLOGIE. By W. Langreder. 293 pages, 135 illustrations. $14.05. Stuttgart: Georg Thieme Verlag, 1961.

AN ATLAS OF BRONCHOSCOPY. By A. Huzly, M.D. 95 pages, 180 illustrations. $12.50. New York and London: Grune & Stratton, Inc., 1960.

INTRA-ABDOMINAL CRISES. By Kenneth D. Keele, M.D., F.R.C.P., and Norman M. Matheson, F.R.C.S., M.R.C.P., F.A.C.S. 379 pages, illustrated. $10.00. Washington, D. C.: Butterworths, 1961.

NEURORADIOLOGY WORKSHOP. VOL. I: SCALP, SKULL, AND MENINGES. By Leo M. Davidoff, M.D., Harold G. Jacobson, M.D., and Harry M. Zimmerman, M.D. 251 pages, 89 illustrations. $16.50. New York and London: Grune & Stratton, Inc., 1961.

THE HUMAN CEREBELLUM; AN ATLAS OF GROSS TOPOGRAPHY IN SERIAL SECTIONS. By Jay B. Angevine, Jr., Ph.D., Elliott L. Mancall, M.D., and Paul I. Yakovlev, M.D. 138 pages, 75 illustrations. Boston: Little, Brown & Co., 1961.

MEDICAL ALMANAC 1961–1962. By Peter S. Nagan, A.B., M.A., M.S. 514 pages, no illustrations. $5.00. Philadelphia and London: W. B. Saunders Co., 1961.

DIE CHIRURGISCHE BEHANDLUNG DER ANGEBORENEN FEHLBILDUNGEN. By Priv.-Doz. Dr. K. Kremer. 583 pages, 349 illustrations. $29.50. Stuttgart: Georg Thieme Verlag, 1961.

CARDIOPERICARDIOMYOPEXY; NEW SURGICAL TREATMENT FOR HEART DISEASE. By Dr. Aaron N. Gorelik in collaboration with others. Rev. English ed. of "La cardiopericardiomyopexie," Expansion Scientifique Francaise, Paris, 1956. 176 pages, 30 illustrations. New York: Myopexy Association Inc., 1960.

FROM GIRLHOOD TO WOMANHOOD. By Albert Sharman, M.D., D.Sc., F.R.C.O.G. 69 pages, 4 illustrations. $1.75. Edinburgh and London: E. & S. Livingstone Ltd., 1960; Baltimore: The Williams & Wilkins Co., exclusive U. S. agents.

DAS CARCINOMA COLLI UTERI SEINE PROGNOSE UND BEHANDLUNG. By Dr. med. Wilhelmine Janisch-Raskovic. 596 pages, 76 illustrations. Leipzig: Georg Thieme, 1960.

AIDS TO SURGICAL ANATOMY. By D. B. MOFFAT, M.B., B.S., F.R.C.S. 5th ed. 211 pages, 54 illustrations. $3.50. London: Baillière, Tindall & Cox, 1960; Baltimore: The Williams & Wilkins Co., exclusive U. S. agents.

711 MEDICAL MAXIMS. By William S. Reveno, M.D. Vol. II. 136 pages, no illustrations. $3.50. Springfield, Ill.: Charles C Thomas, 1961.

TUMORS OF THE FEMALE SEX ORGANS. Part 3: Tumors of the Ovary and Fallopian Tube. By Arthur T. Hertig, M.D., and Hazel Gore, M.B., B.S. 176 pages, 157 illustrations. $1.40. Washington, D. C.: Armed Forces Institute of Pathology, 1961.

AMERICAN COLLEGE OF SURGEONS

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PRELIMINARY PLANS FOR THE 47TH CLINICAL CONGRESS CHICAGO, ILLINOIS, 2 THROUGH 6 OCTOBER 1961

CHICAGO, popular convention city, will be host to this year's Congress. Now a leading medical center, with 5 medical schools, 72 accredited hospitals, and headquarters offices for several allied medical organizations, this city has become a focal point for research and education in the medical field.

Visitors to this Congress—the thirteenth to be held in Chicago since 1910—will find much of both scientific and recreational interest in this giant midwest city. Chicago is known for fine hotels, museums and shops, as well as being a center of transportation, steel production, home furnishings, construction, printing and publishing, graphic arts, and other industries.

The Conrad Hilton, overlooking Lake Michigan, will be headquarters for registration, Ciné Clinics, color television, motion pictures, scientific sessions, some Postgraduate Courses, and scientific and industrial exhibits. Additional sessions will be in nearby hotels.

The program will be developed in this Journal in the next three issues. This issue lists some advance information for your consideration.

Committee on Arrangements

John T. Reynolds, Associate Clinical Professor of Surgery, University of Illinois, is Chairman of the Advisory Committee on Local Arrangements. He is assisted by the following Chicago Fellows of the College: Sam W. Banks, T. Howard Clarke, John W. Curtin, Frederic A. de Peyster, Joseph P. Evans, Donald J. Ferguson, W. James Gillesby, Paul V. Harper, Ellsworth E. Hasbrouck, Myron M. Hipskind, Ormand C. Julian, John L. Keeley, F. John Lewis, James W. Merricks, Harold L. Method, Peter V. Moulder, Jr., Frank W. Newell, Frederick W. Preston, Daniel W. Ruge, Edward F. Scanlon, Charles A. Schiff, Robert L. Schmitz, Harry W. Southwick, and John R. Wolff. With Dr. Moulder as Chairman, the Subcommittee on Press Relations consists of Drs. Clarke, de Peyster, Hipskind, Julian, Keeley, Lewis, Method, Ruge, Schiff, and Southwick.

Evening Meetings

Only two evening sessions are planned this year, that of the Motion Picture Symposium, scheduled for Tuesday evening, and the Convocation evening, on Thursday. Robert M. Zollinger, incoming President, will give his address on Thursday evening, and initiates will be inducted into Fellowship. The Martin Memorial Lecture, formerly heard Monday evening, has been changed to Thursday afternoon.

Television, Ciné Clinics, Motion Pictures

Smith, Kline & French Laboratories will again present on-the-spot telecasts of operations performed at Albert Merritt Billings Hospital of the University of Chicago. Paul V. Harper, Chicago, is local television chairman and Edwin H. Ellison, Milwaukee, is national chairman. American Cyanamid Company, Surgical Products Division, will again sponsor new ciné clinic films, under the chairmanship of Hilger P. Jenkins, Chicago, and the College's Motion Picture Committee.

Trauma Oration and Baxter Lecture

Preston A. Wade, Clinical Professor of Surgery, Cornell University Medical College, and member of the College's Trauma Committee since 1947, will give the Trauma Oration on Wednesday afternoon. On Monday afternoon Francis D. Moore, Moseley Professor of Surgery, Harvard Medical School, will give the Baxter Lecture, endowed since 1957 by Baxter Laboratories and given by an authority in the field of parenteral therapy.

Postgraduate Courses

Among the nine Postgraduate Courses to be given this year are two new titles: Injury of the Joints of the Upper Extremity and Cancer Chemotherapy. Because of the popularity of these seminars, early registration is suggested, for admission will be by ticket only. Courses and chairmen follow:

Pre- and Postoperative Care. JAMES D. HARDY, Jackson, Mississippi.
Gastrointestinal Diseases. STANLEY O. HOERR, Cleveland.
Diseases of the Liver, Biliary Tract, Pancreas. BEN EISEMAN, Denver.
Cardiovascular Surgery. IVAN W. BROWN, Durham.
Injury of the Joints of the Upper Extremity. SAM W. BANKS, Chicago.
Obstetrics and Gynecology. DAVID DANFORTH, Evanston.
Cancer Chemotherapy. HARRY S. MORTON, Montreal.
Thoracic Surgery. HIRAM T. LANGSTON, Chicago.
Recent Advances in Pediatric Surgery. H. WILLIAM CLATWORTHY, JR., Columbus.

Forum on Fundamental Surgical Problems

The Forum Committee, headed by William P. Longmire, Jr., Los Angeles, will present approximately 258 reports covering recent developments in surgical research and techniques.

Scientific and Industrial Exhibits

The Scientific Exhibition Committee, headed by George W. Stephenson, Assistant Director of the College, will display results of recent study by research teams and surgical departments from medical centers throughout the country.

Mr. Thomas E. McGinnis, Administrative Assistant-Manager, Exhibits and Meeting Arrangements, is in charge of Industrial Exhibits, and inquiries regarding applications and space may be addressed to him at the American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois.

Advance Registration

Fellows are now receiving the Clinical Congress Invitation Brochure, containing information about hotels, Postgraduate Courses, travel, and registration forms. This brochure is available to non-Fellows upon request. Early registration is advised for first choice of courses, hotels, and travel accommodations.

Fellows whose dues are paid to 31 December 1960 pay no registration fee. Those whose dues are not paid as of that date pay $40.00. Non-Fellows pay $40.00 if registered Sunday, Monday, or Tuesday; $30.00 if registered Wednesday; $20.00 if registered Thursday; $10.00 if registered Friday. Members of the Federal Services will pay half of the above schedule of fees. No fee (except for a Postgraduate Course) is required of initiates, members of the candidate group, and surgical residents. Everyone who attends a Postgraduate Course pays a $10.00 fee.

Wives Invited

The Ladies' Entertainment Committee is planning a week of enjoyable activities, and doctors' wives are cordially invited.

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*U.S.A. and Foreign Pat. Pend.

1. Cock, T. C., *et al.:* California Med. *89*:257, 1958.
2. Bertrand, J. J., *et al.:* Vox Sanguinis *4*:385, 1959.

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references

(1) Pareira, M. D., *et al.*: J.A.M.A. *156*:810-816 (Oct. 30) 1954.
(2) Winkelstein, A.: Am. J. Gastroenterol. *27*:45-52 (Jan.) 1957.

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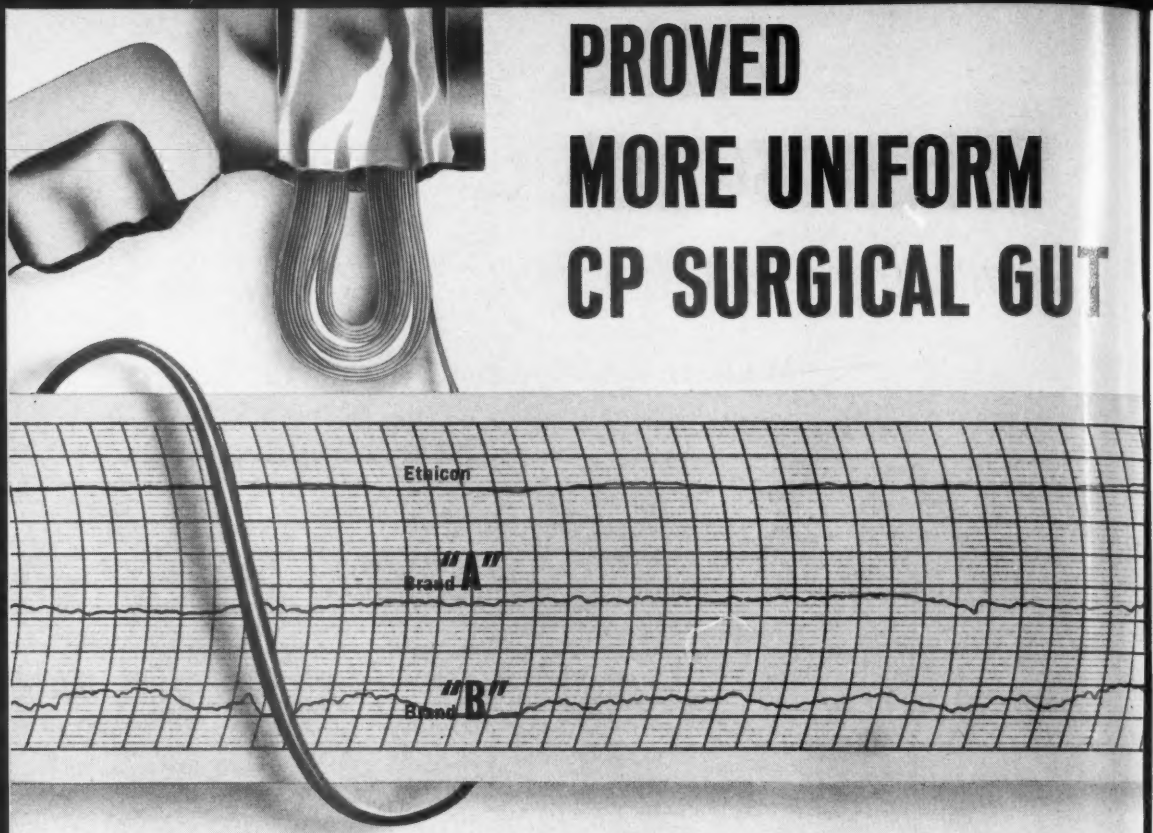

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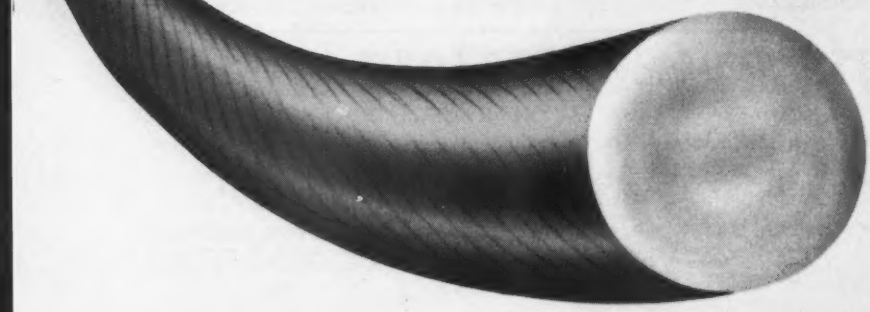

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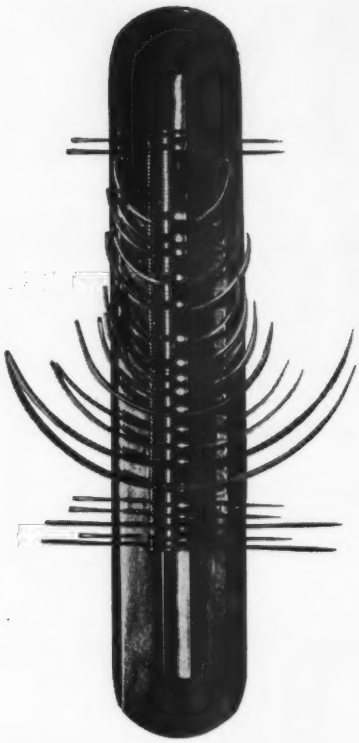

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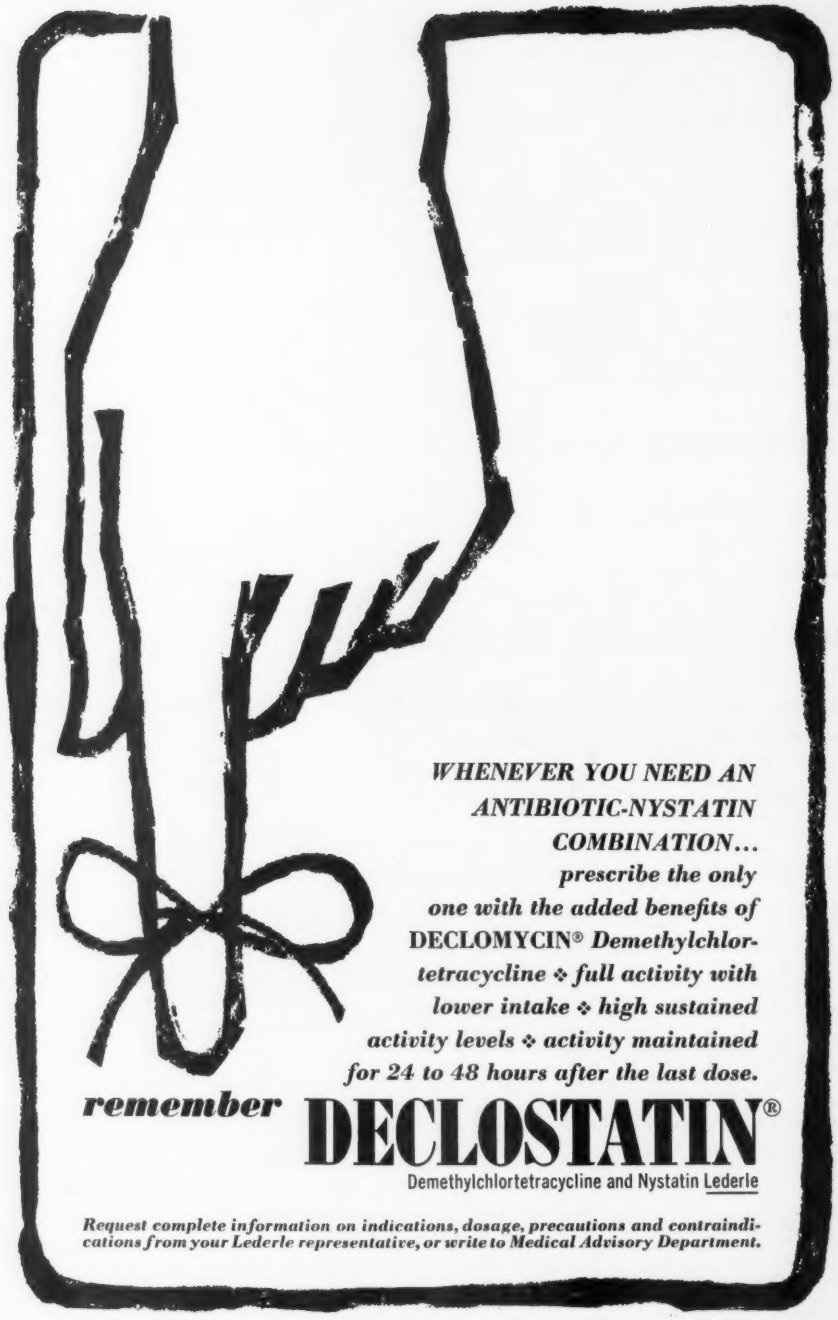

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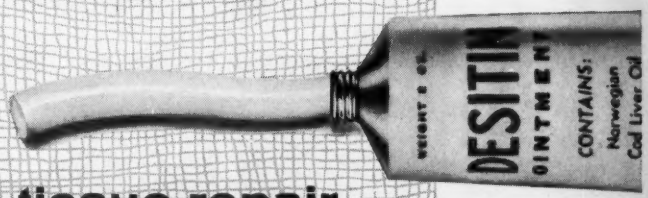

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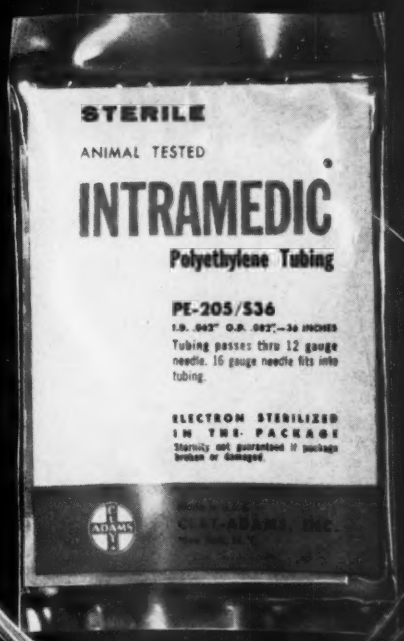

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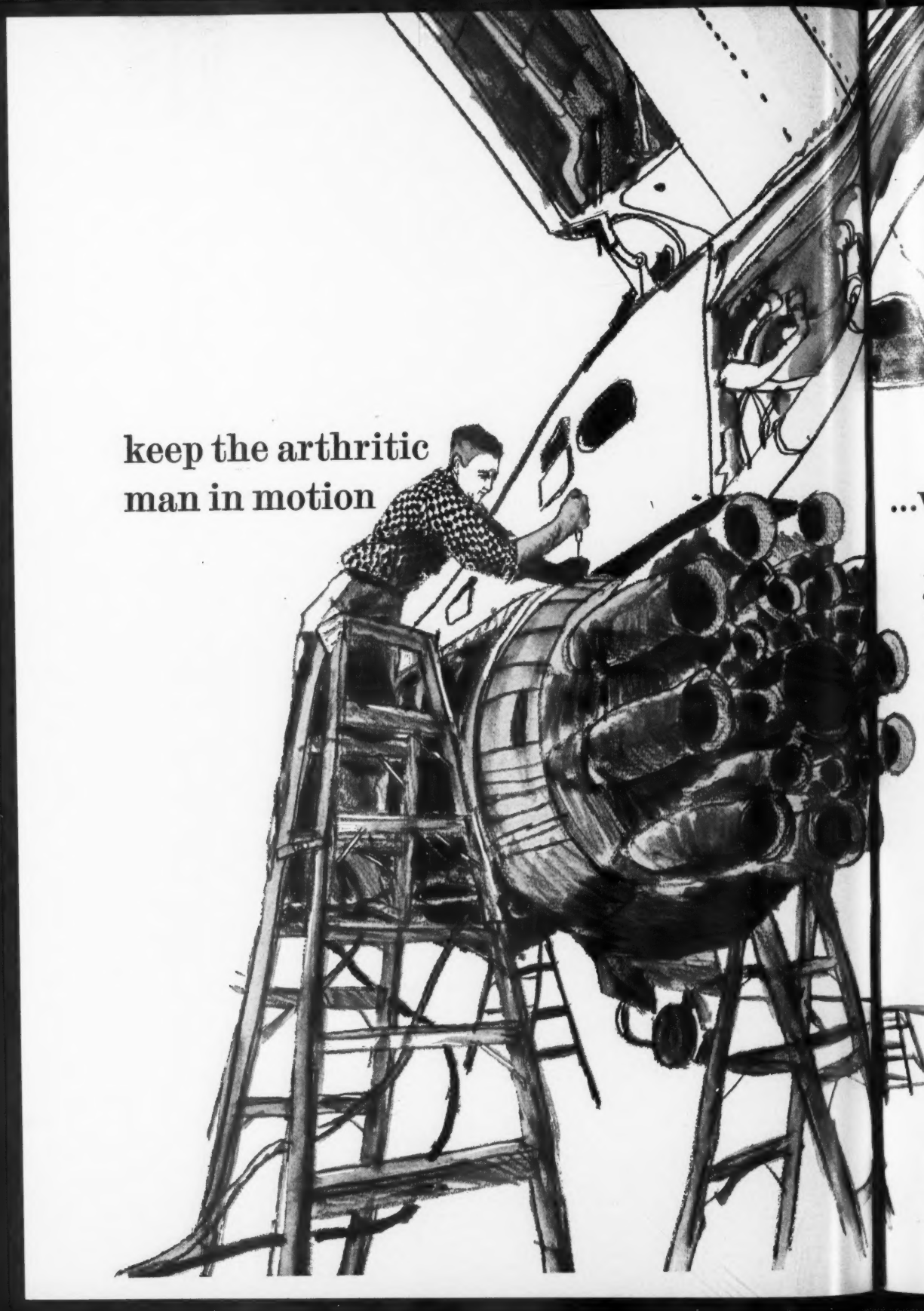
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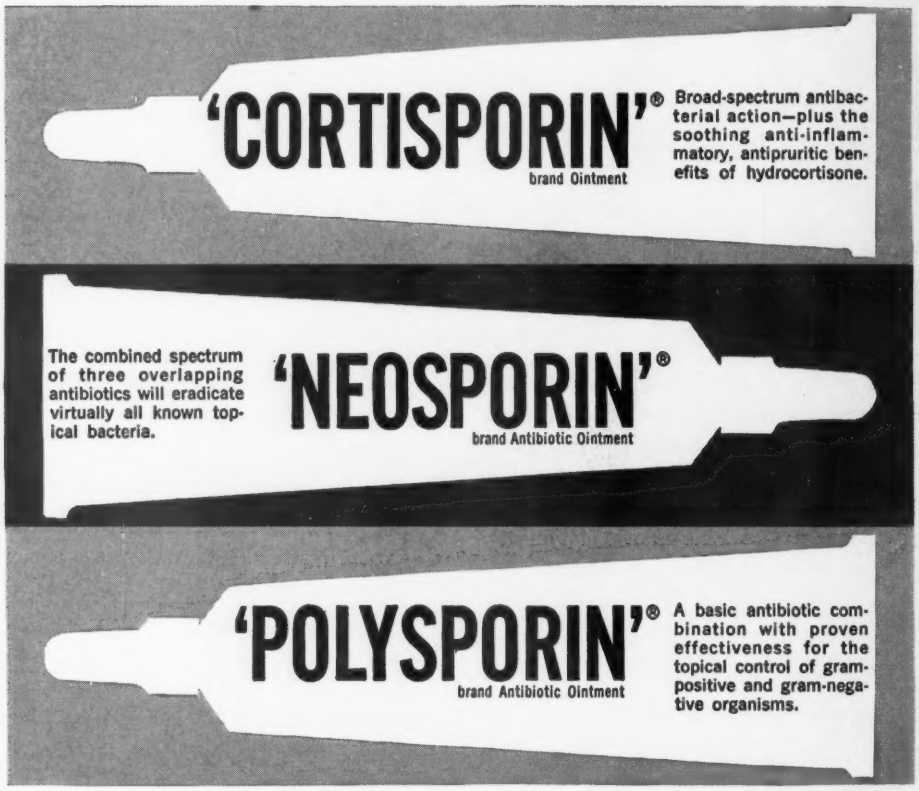
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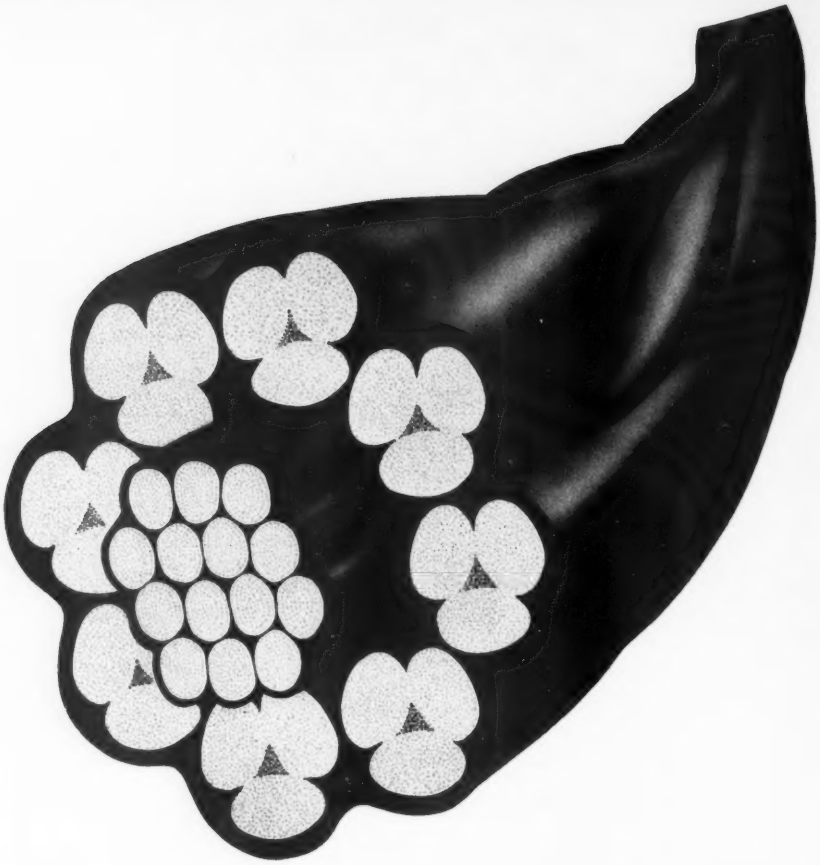

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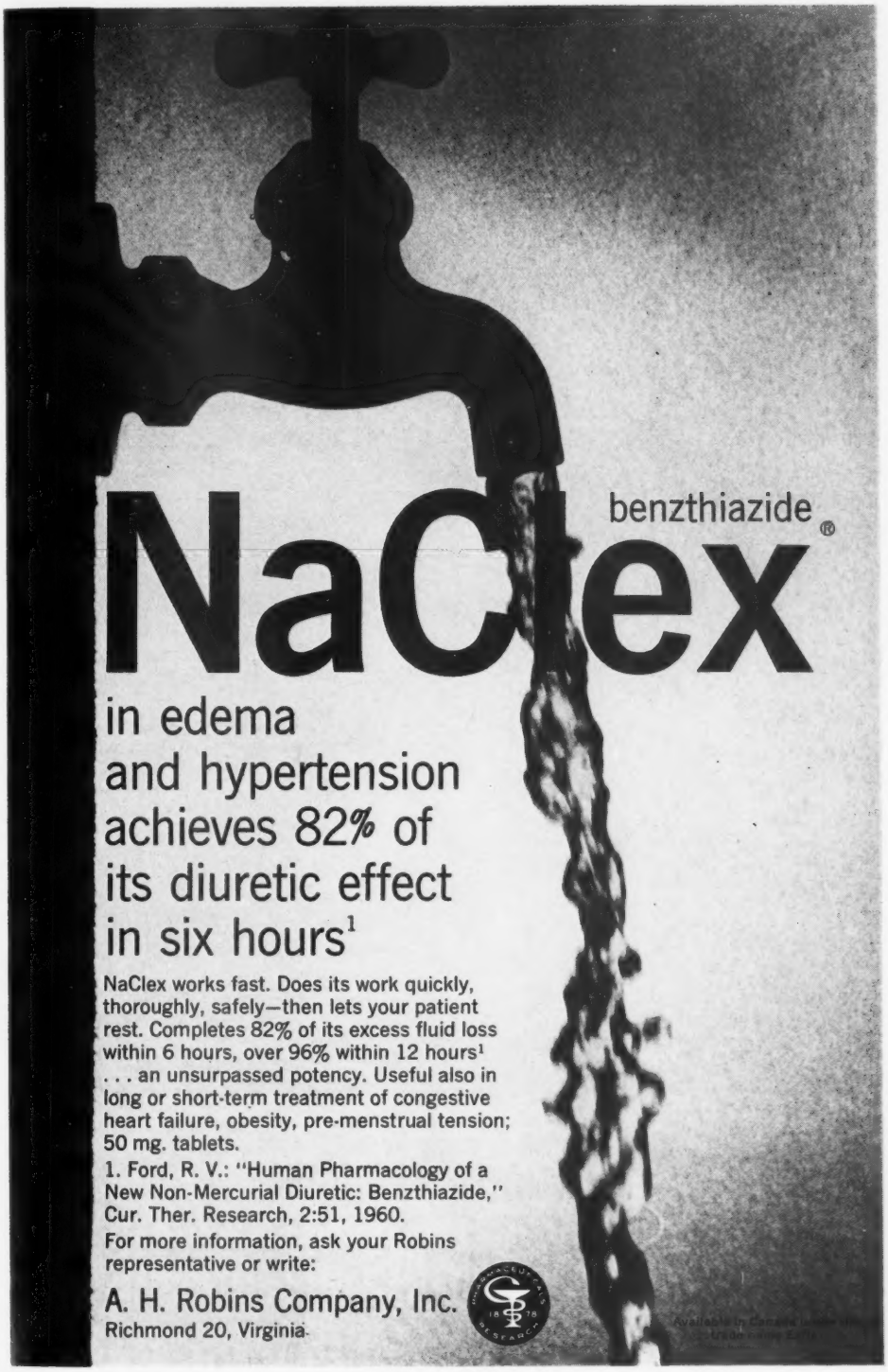
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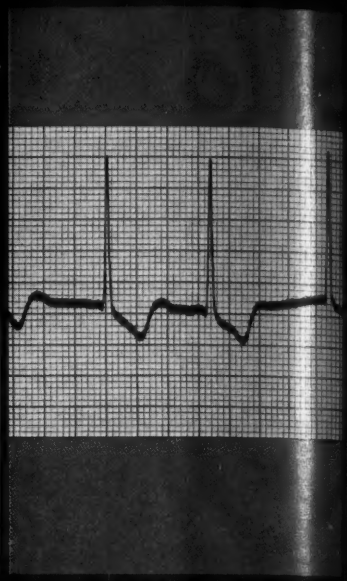
NaClex works fast. Does its work quickly, thoroughly, safely—then lets your patient rest. Completes 82% of its excess fluid loss within 6 hours, over 96% within 12 hours[1] . . . an unsurpassed potency. Useful also in long or short-term treatment of congestive heart failure, obesity, pre-menstrual tension; 50 mg. tablets.
1. Ford, R. V.: "Human Pharmacology of a New Non-Mercurial Diuretic: Benzthiazide," Cur. Ther. Research, 2:51, 1960.
For more information, ask your Robins representative or write:
A. H. Robins Company, Inc.
Richmond 20, Virginia

*before treatment**

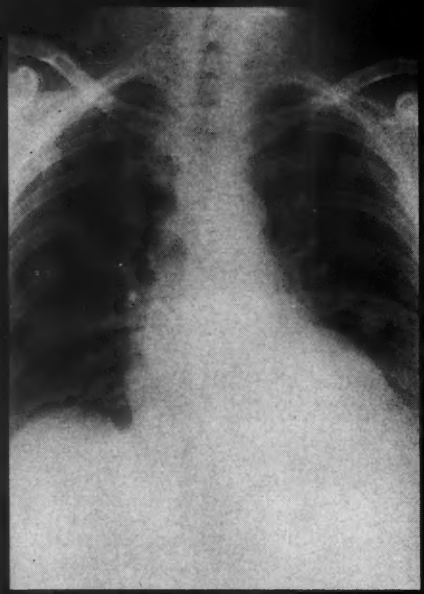
Cardiac enlargement and pulmonary congestion.



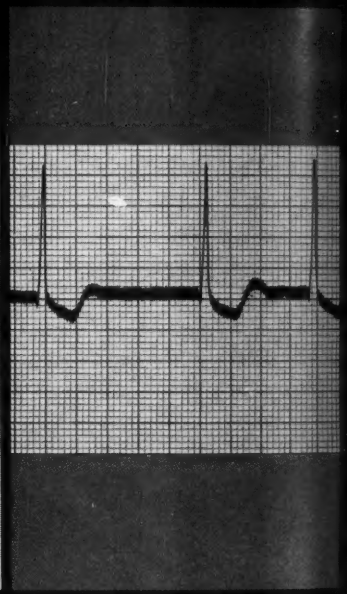
Left ventricular strain and hypertrophy (ST depression in Lead V4).

after one month on

HYDROPRES*



Reduction in heart size and clearing of congestion.



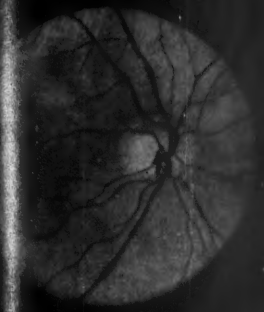
Changes toward normal (less ST depression).

*case report

effective by itself in many hypertensives...
indicated in all degrees of hypertension

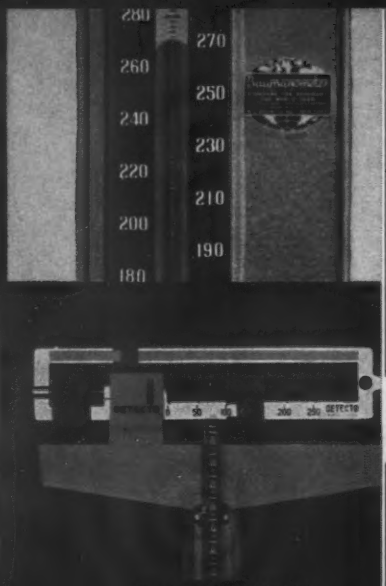
HYDROPRES®

HYDRODIURIL® HYDROCHLOROTHIAZIDE with RESERPINE

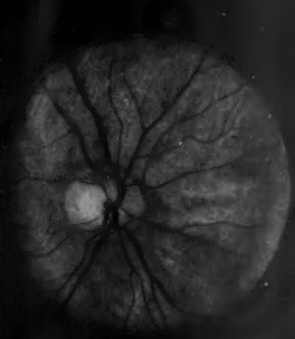


Hypertensive retinopathy with hemorrhages.

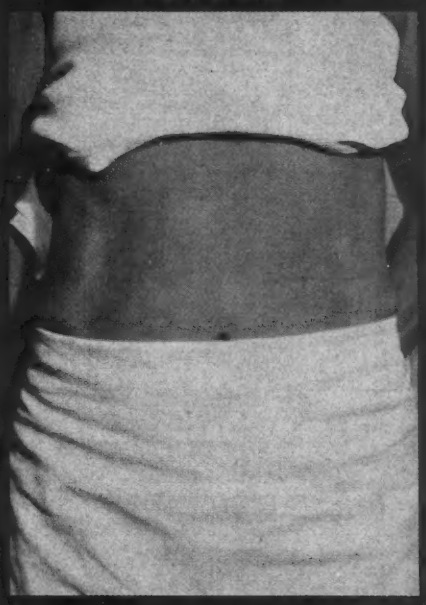
Liver palpable 5 fingerbreadths below costal margin.



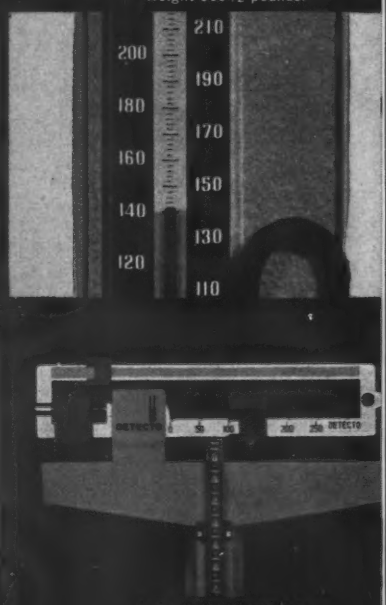
Blood pressure 270/120.
Weight 110½ pounds.



Very little change.



Liver not palpable.



Blood pressure 140/72.
Weight 105 pounds.

HYDROPRES-25

25 mg. HydroDIURIL hydrochlorothiazide, 0.125 mg. reserpine per tablet. One tablet one to four times a day.

HYDROPRES-50

50 mg. HydroDIURIL hydrochlorothiazide, 0.125 mg. reserpine per tablet. One tablet one or two times a day.

also available:

HYDROPRES-Ka†-25

25 mg. HydroDIURIL hydrochlorothiazide, 0.125 mg. reserpine, 572 mg. potassium chloride (equivalent to 300 mg. potassium) per tablet.

HYDROPRES-Ka†-50

50 mg. HydroDIURIL hydrochlorothiazide, 0.125 mg. reserpine, 572 mg. potassium chloride (equivalent to 300 mg. potassium) per tablet.

It is essential to reduce the dosage of other antihypertensive agents, particularly the ganglion blockers, by at least 50 per cent immediately upon addition of these agents or of HYDROPRES Tablets to the regimen.

Before prescribing or administering HYDROPRES, the physician should consult the detailed information on use accompanying the package or available on request.

MSD MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.

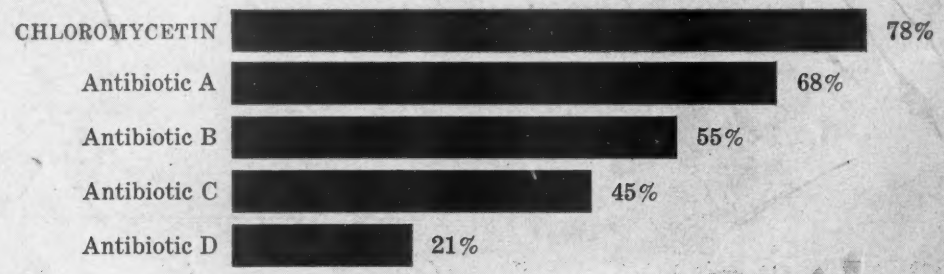
†HYDROPRES, HYDROPRES-Ka, AND HYDRODIURIL ARE TRADEMARKS OF MERCK & CO., INC.

inside as well as outside the hospital... staphylococci usually remain sensitive to

CHLOROMYCETIN®

(chloramphenicol, Parke-Davis)

IN VITRO SENSITIVITY OF 250 STRAINS OF STAPHYLOCOCCI TO CHLOROMYCETIN AND TO FOUR OTHER ANTIBIOTICS*



These strains of coagulase-positive staphylococci were isolated from hospitalized patients at a large county hospital during the year 1959. Sensitivity tests were done by the disc method.

*Adapted from Bauer, A. W.; Perry, D. M., & Kirby, W. M. M.: *J.A.M.A.* 173:475, 1960.

Warning: Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after short-term and with prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective, or in the treatment of trivial infections such as colds, influenza, viral infections of the throat, or as a prophylactic agent.

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied upon to detect bone marrow depression prior to development of aplastic anemia.

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in various forms, including Kapseals® of 250 mg., in bottles of 16 and 100. See package insert for details of dosage and administration. 51361

PARKE-DAVIS

PARKE, DAVIS & COMPANY, Detroit 32, Michigan

Put your low-back patient back on the payroll

Soma relieves stiffness —stops pain, too

YOUR CONCERN: Rapid relief from pain for your patient. Get him back to his normal activity, fast!

HOW SOMA HELPS: Soma provides direct pain relief while it relaxes muscle spasm.

YOUR RESULTS: With pain relieved, stiffness gone, your patient is soon restored to full activity—often in days instead of weeks.

Kestler reports in controlled study: *Average time for restoring patients to full activity: with Soma, 11.5 days; without Soma, 41 days.* (*J.A.M.A. Vol. 172, No. 18, April 30, 1960.*)

Soma is notably safe. Side effects are rare. Drowsiness may occur, but usually only in higher dosages. Soma is available in 350 mg. tablets. **USUAL DOSAGE:** 1 **TABLET Q.I.D.**

The muscle relaxant with an independent pain-relieving acti

SOMA®

(carisoprodol, Wallac

Wallace Laboratories, Cranbury, New Jers

Greater Economy...Efficiency

DAVOL® 3P* Disposables

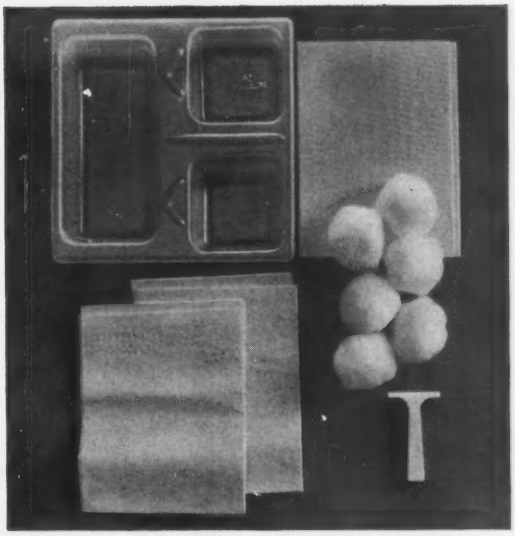
*3P: Personal Patient Protection

A new line of labor-saving disposables involving mass daily routines.

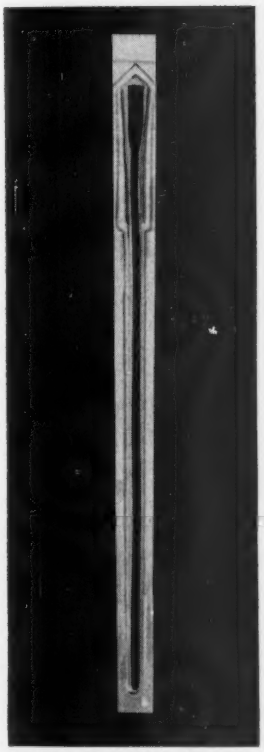
SAFE: Reduce the danger of cross-infection.

ECONOMICAL: Eliminate time-and-labor expense of autoclaving hospital-prepared sets.

CONVENIENT: Pre-packed, compact: can be stored in quantities in floor utility rooms—ready for immediate use when and where needed.



DISPOSABLE PREP SET • Multi-Cupped Tray • Razor (with blade) • 2 Absorbent Towels • 6 Cotton Balls • Plastic-Coated Towel • Plastic Cover



STERILE DISPOSABLE RUBBER CATHETER • New low price! • All purpose—combines the desirable features of the Nelaton and Robinson style catheters • May also be used as aspirating catheter

STERILE DISPOSABLE CATHETERIZATION SET • Contains: New All-Purpose **Rubber** Catheter for use where 14 or 16 French is desired • Multi-cup Plastic Tray • New Plastic Specimen Bag with Identification Tag • Davol Lubraseptic Jelly • 5 Cotton Balls • Plastic Gloves • Plastic-Coated Towel • Fenestrated Towel • Tray Cover

For complete information please write on your Professional or Institutional letterhead to:

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Lilly

a powerful ally to specific therapy

Becotin-T®

■ *"In severe injury or illness there is a large increase in utilization or destruction of vitamins within the body."*

McLester, J. S., and Darby, W. J.: Nutrition and Diet in Health and Disease, Ed. 6, p. 569. Philadelphia: W. B. Saunders Company, 1952.

Specifically designed to assist in medical or surgical aftercare

Becotin-T helps shorten convalescence by restoring normal tissue levels of important water-soluble vitamins depleted by the stress of severe injury or illness.

There's a "loading dose" in every tablet.

Each Becotin-T tablet contains:

Thiamine Mononitrate (B_1)	15 mg.
Riboflavin (B_2)	10 mg.
Pyridoxine Hydrochloride (B_6)	5 mg.
Nicotinamide	100 mg.
Pantothenic Acid (as Calcium Pantothenate, Racemic)	20 mg.
Vitamin B_{12} (Activity Equivalent)	4 mcg.
Ascorbic Acid (as Sodium Ascorbate) (C)	300 mg.
Liver Preparation and Stomach-Tissue Material, Desiccated, Lilly	125 mg.

Usual Dosage: 1 or 2 tablets daily.

Lilly Vitamins . . . "The Physician's Line"

Becotin-T® (vitamin B complex with vitamin C, therapeutic, Lilly) 108814

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POSITIVE*

SEPARATION OF THE FETAL AND MATERNAL

ECG

WITH THE

FETAL HEART MONITOR

PROVIDES CONSTANT ELECTRONIC MONITORING OF FETUS DURING LABOR AND DELIVERY

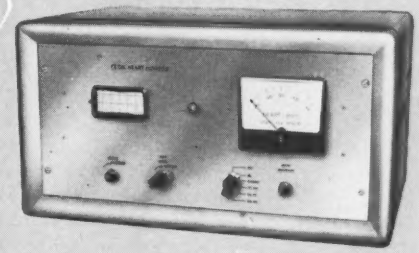
Through electronics, the *Fetal Heart Monitor* provides a complete isolation of the fetal heart rate from the maternal rate . . . during labor and delivery. An electrode of spring steel attaches to the fetus' scalp with the electronic circuit completed with two standard, plate-type electrodes. The electrode may be left attached for hours with no difficulty or distress to the fetus or mother.

INSTANT RECOGNITION OF FETAL DISTRESS

During labor and delivery the obstetrician receives a positive signal from the fetus both *during* and *between* contractions. This constant, accurate fetal rate can be observed on the heart rate meter and oscilloscope and may be heard through speakers. A permanent record of rate tracing can be made by attaching to any standard electrocardiograph.

ELECTRODE EASILY PLACED

Surgically sharp points are brought together on a fold of fetal scalp by moving a sliding sleeve. Electrode is detachable for sterilization in an autoclave.



Write for brochure or additional information.

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CORPORATION
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* A Technic for Recording Fetal ECG During Labor and Delivery by Chas. A. Hunter, Jr., M. D., et al. 16:567, 1960. Obst. and Gynec.

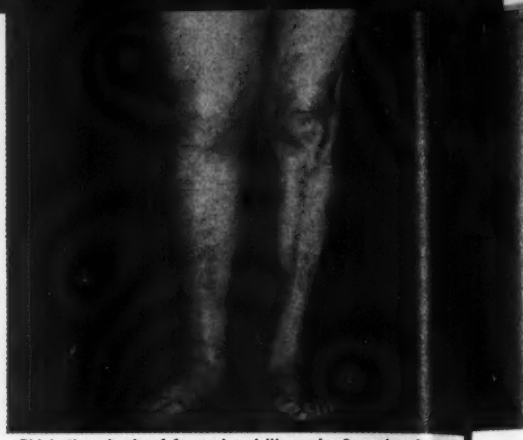
BEFORE

LYOVAC®

THROMBOLYSIN®

FIBRINOLYSIN (HUMAN)

a new agent
for lysis of
vascular thrombi

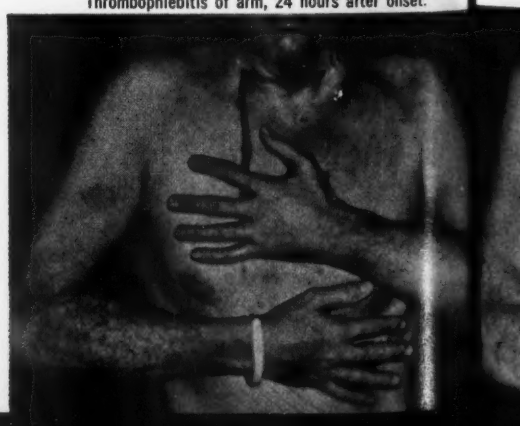


Phlebothrombosis of femoral and iliac vein, 3 weeks after onse

Superior vena cava thrombosis (8 hrs. after starting THROMBOLYSI

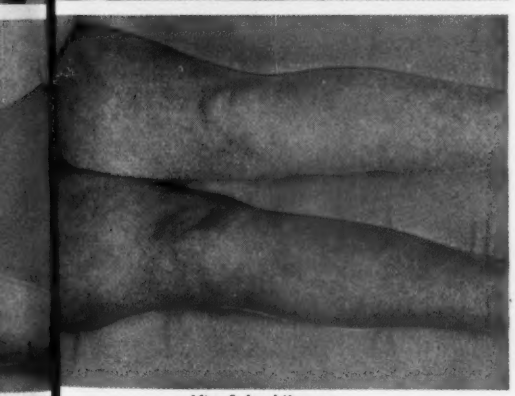
Phlebothrombosis (8 weeks' duration in left leg, 6 weeks' in right

Thrombophlebitis of arm, 24 hours after onset.



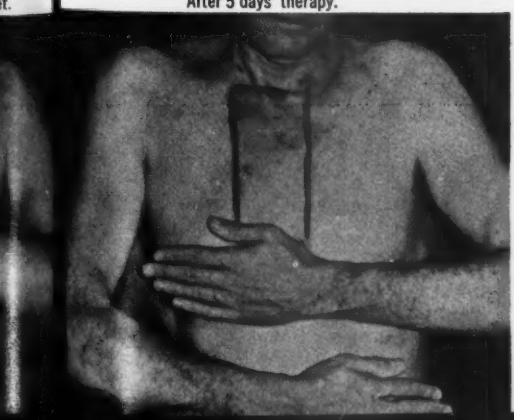
After 6 days' therapy.

After 3 days' therapy.



After 6 days' therapy.

After 5 days' therapy.



AFTER LYOVAC® THROMBOLYSIN®

FIBRINOLYSIN (HUMAN)

in thrombophlebitis, phlebothrombosis, pulmonary embolism, and certain arterial thrombi*, LYOVAC® THROMBOLYSIN makes possible

- lysis of formed clots
- reduced mortality and morbidity, shortened hospitalization
- reduced incidence of postphlebitic complications

with decreased incidence of reactions such as fever, chills, or malaise of severe proportions; higher degree of safety; greater, more predictable potency.

Supply: Each bottle contains 50,000 MSD units.

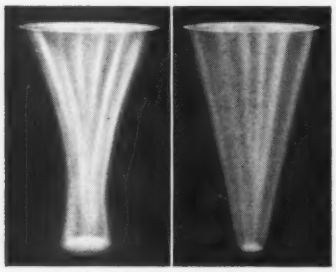
*See package circular for qualifications concerning cerebrovascular accidents and myocardial infarction.

Before prescribing or administering THROMBOLYSIN, *the physician should consult the detailed information on use accompanying the package or available on request.*

MERCK SHARP & DOHME
DIVISION OF MERCK & CO., INC., WEST POINT, PA.

LYOVAC AND THROMBOLYSIN ARE TRADEMARKS OF MERCK & CO., INC.

Castle "600 Series" Floods the Wound with Near Shadowless Light



Beams from single reflector (right) tend to be more parallel, easily blocked; focal range is relatively narrow, requiring constant adjustment. By contrast, Castle Multi-Beam Light (left) is always in proper focus; gives unsurpassed shadow reduction.

There's no objectionable shadowing of the wound when heads and hands interfere. That's because a "600 Series" Light has FOUR MULTI-STEP REFLECTORS. Together they illuminate from 112 different angles; bypass obstructions with ease. What's more, there's a Center Spotlight built into the lamp's center to boost total intensity for extra deep work.

This Multi-Beam optical system is unique! Light is delivered from so many directions that only a fraction of the total illumination is ever interrupted by surgical procedure. The pattern stays constant—you see better. Multi-Beam optics virtually eliminate glare, too, and provide unsurpassed depth of focus. Five separate bulbs provide protection—there's little chance of simultaneous burnout. Ask your dealer about Castle "600 Series" Lights, or write for catalog.

Castle

WILMOT CASTLE COMPANY, 2206 E. HENRIETTA RD., ROCHESTER 18, N.Y.

Subsidiary of Ritter Company Inc.

Again
in Tri

Afte
Cer

Sultrin CREAM

TRADEMARK (TRIPLE SULFA CREAM—WF*)

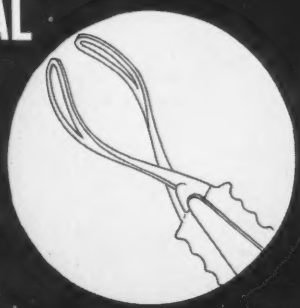
Against Secondary Invaders in Trichomoniasis

In Nonspecific Vaginitis

NEW WHITE FORMULATION FOR LOCAL CERVICOVAGINAL THERAPY

After Cervical Cauterization, Cervical or Vaginal Surgery

White SULTRIN Cream, formerly available in buff-colored Triple Sulfa Cream, destroys a wide variety of vaginal pathogens and even helps eradicate "difficult" trichomonads by restoring the normal vaginal pH. Outstandingly effective in many obstetric and gynecologic conditions, this triple sulfonamide cream promotes rapid healing, relieves inflammation, minimizes discomfort, and significantly reduces odor and discharge. Supplied: 78 Gm. tube with or without applicator. Also available: SULTRIN Triple Sulfa Vaginal Tablets.



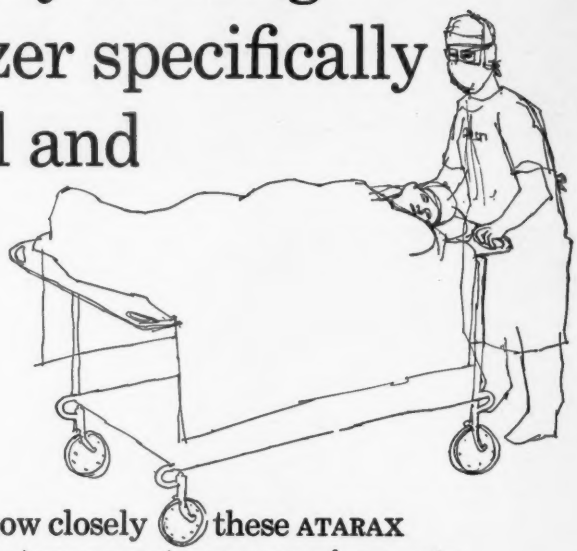
In Postpartum Care

*WHITE FORMULATION

ACTIVE INGREDIENTS: SULFATHIAZOLE 3.42%, SULFACETAMIDE 2.86%, N^1 BENZOYLSULFANILAMIDE 3.7%, AND UREA 0.64%

Ortho

how would you design a tranquilizer specifically for surgical and obstetrical patients?



wouldn't you want it to: see how closely these ATARAX advantages meet your requirements

decrease the need for narcotic pre-medication	"Hydroxyzine hydrochloride [ATARAX] appeared to have . . . a useful influence upon the course of narcosis. The doses of the usual drugs could be reduced by about 30%."[1]
relieve anxiety connected with labor	ATARAX ". . . is a valuable compound for relief of stress and apprehension . . . helps the patient to manage her own labor."[2]
calm without significantly depressing vital function	ATARAX ". . . produces an ideal preoperative state without depression of vital functions."[3]

ATARAX is remarkably well tolerated. Why not extend its benefits to *all* your tense and anxious patients?

Dosage: Atarax parenteral: Pre- and postoperative adjunctive medication: Adults—I.M. or I.V., 25-100 mg.; children—I.M., 0.5 mg./lb. body weight. *Pre- and postpartum adjunctive therapy:* I.M. or I.V., 25-100 mg. The usual precautions pertaining to parenteral therapy should be observed. *Atarax tablets or syrup:* Adults—25 mg. t.i.d. to 100 mg. q.i.d. Children—under 6 years, 50 mg. daily; over 6 years, 50-100 mg. daily; in divided doses. Prescription only.

References: 1. Ponzi, A.: Minerva anestesiol. *22*:306 (Sept.) 1956. 2. Sicuranza, B. J., Tisdall, L. H.: Postgrad. Med. *28*:558 (Nov.) 1960. 3. Grady, R. W., and Rich, A. L.: J. M. A. Alabama *29*:377 (Apr.) 1960.

ATARAX®

PASSPORT TO TRANQUILITY

(brand of hydroxyzine HCl)

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Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being®

VITERRA® Capsules—Tastitabs®—Therapeutic Capsules for vitamin-mineral supplementation

advancing with surgery

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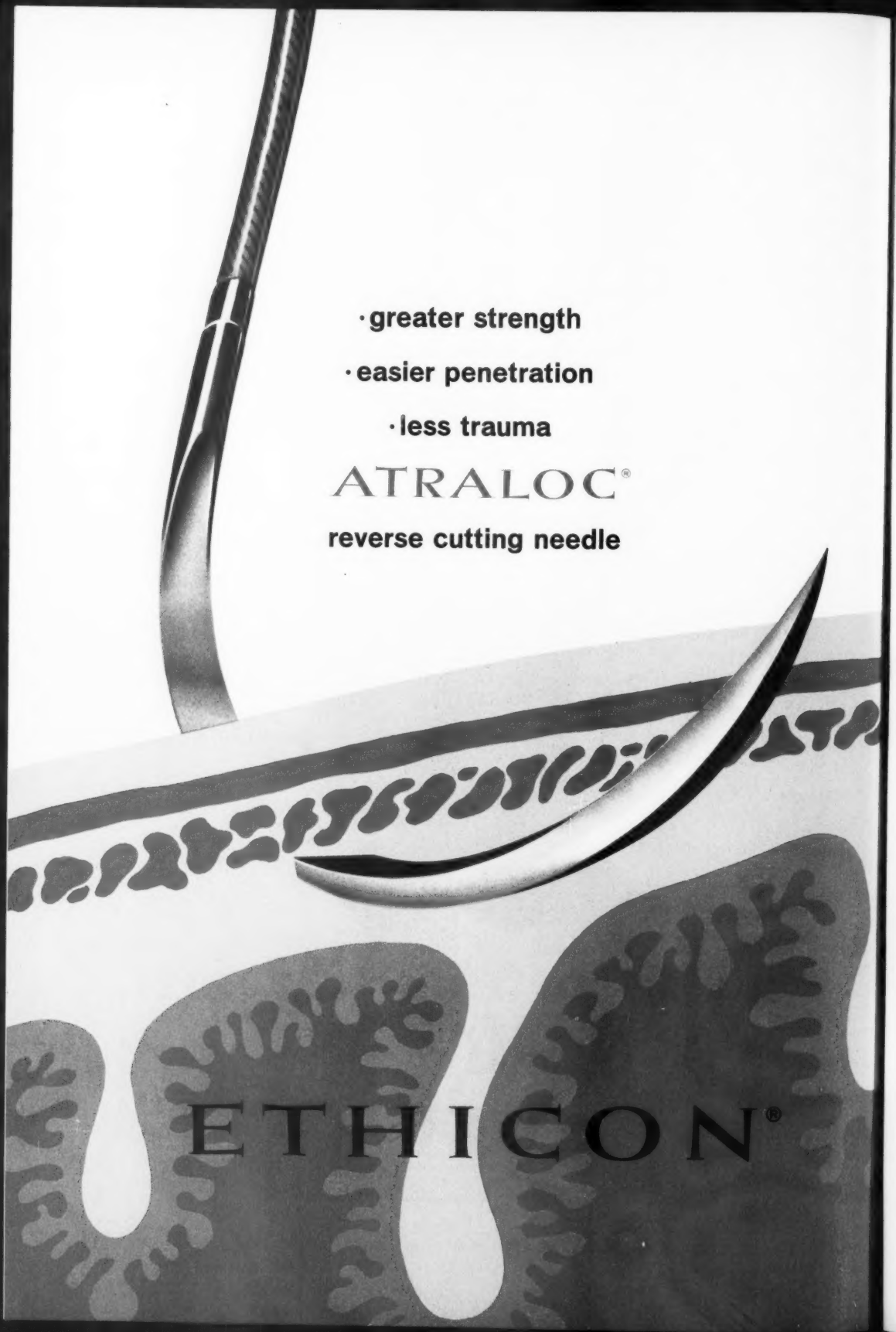
·greater strength
·easier penetration
·less trauma
ATRALOC®
reverse cutting needle
ETHICON®

In trichomonas vaginitis
"...permanent **CURES** in 84.6%"[1] ■ "...symptomatic and bacteriologic **CURES**" in 100%[2] ■ "symptomatic **CURE** was obtained in 100%, and bacteriologic **CURES** in 82.5%"[3]
In moniliasis "symptomatic **CURE** was effected in about 80%"[4]
In mixed infections "complete symptomatic and bacteriologic **CURES** in 92%"[3]
In endocervicitis 75% "were clinically and bacteriologically (as indicated by vaginal smears and cultures) **CURED**"[5]

AVC IMPROVED CREAM/SUPPOSITORIES

STOPS THE TORMENT
DESTROYS THE CAUSE

CURES[1-5]

Vaginitis (trichomonal, monilial, nonspecific), Cervicitis

Each tube contains: 9-aminoacridine hydrochloride 0.2%, sulfanilamide 15.0%, allantoin 2.0%, with lactose in a water-miscible base buffered with lactic acid to pH 4.5. Each AVC Suppository is equivalent to one applicatorful of AVC Improved Cream.

References: 1. Angelucci, H. M.: Am. J. Obst. & Gynec. 50:336, 1945. 2. Hensel, H. A.: Postgrad. Med. 8:293, 1950. 3. Cortese, J. T.: Clin. Med. 2:45, 1955. 4. Dill, L. V., and Martin, S. S.: M. Ann. District of Columbia 17:389, 1948. 5. Horoschak, A., and Horoschak, S.: J. M. Soc. New Jersey 43:92, 1946.

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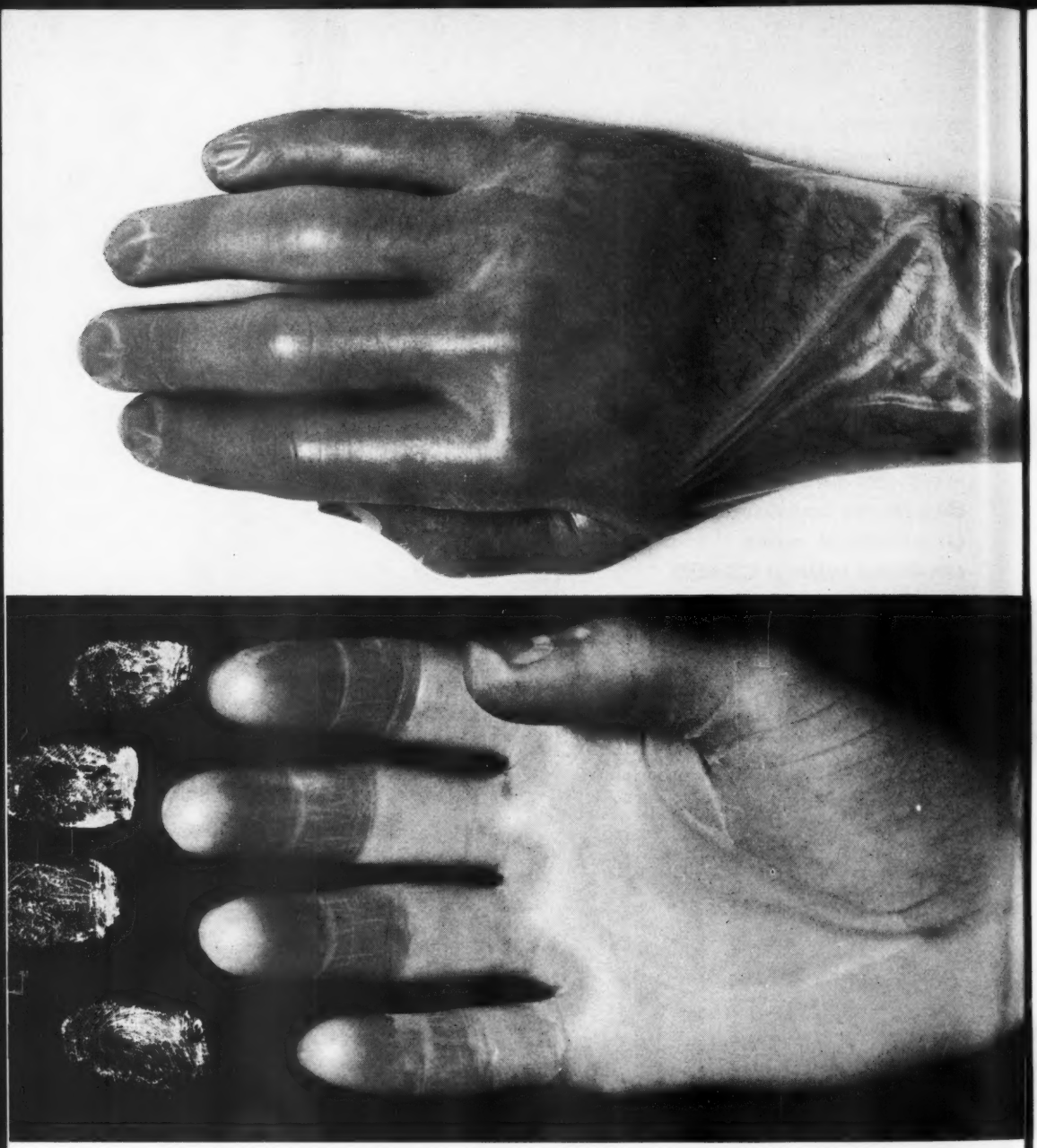
Trademark: AVC AVC-739/60



Fingerprints through an examination glove?

Yes...it actually can be done! Such sensitivity is yours for the first time in the new **WILSON TRU-TOUCH*** Disposable Vinyl Examination Glove - the most sensitive finger-tips next to your own. Non-constricting ...seam-free construction. In a marketing study, more physicians preferred Tru-Touch to conventional examination gloves. A product of **BECTON, DICKINSON AND COMPANY, RUTHERFORD, N. J.**

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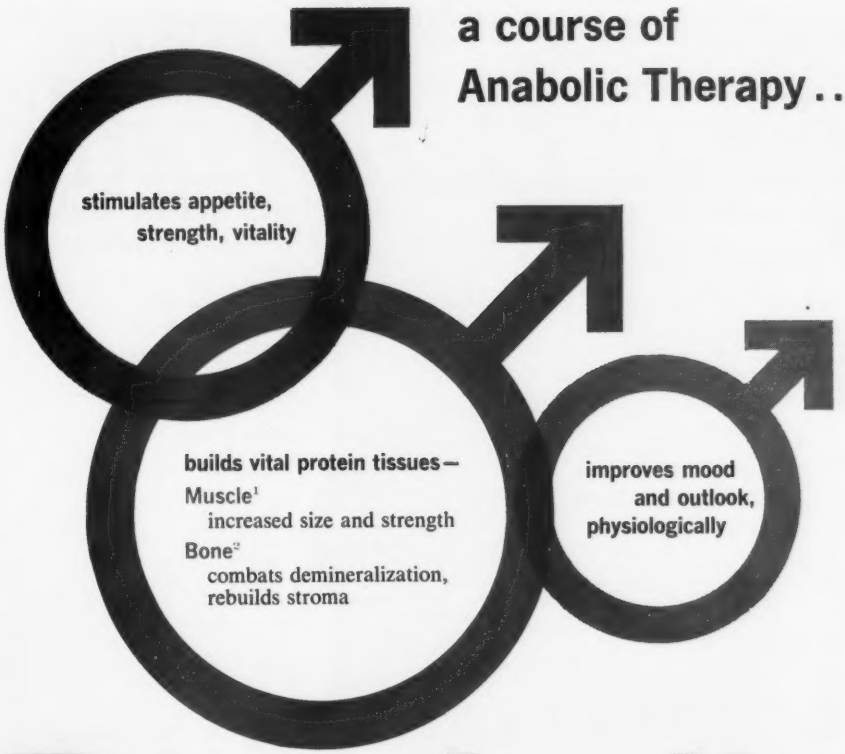

Durabolin®

(nandrolone phenpropionate injection, Organon)

the safest and most potent sustained anabolic therapy

1. *virtually free of virilizing effects*
2. *sustained over 7-14 days*
3. *under your direct control*
4. *no adverse effect on liver function*

to improve mood and outlook; restore appetite, strength and vitality; relieve pain; stimulate gain in solid muscular weight; hasten recovery. Your patient *feels* better because he *is* better.

Indications: anorexia, chronic fatigue and post-viral debility, osteoporosis, mammary cancer, pre- and post-surgery, severe burns and trauma, and other catabolic conditions.

Supplied: DURABOLIN (25 mg. nandrolone phenpropionate/cc.) in 5-cc. vials and 1-cc. ampuls (box of 3). **New Durabolin-50** (50 mg. nandrolone phenpropionate/cc.) in 2-cc. vials.

Dosage: Adults: 50 mg., i.m.; then 25 to 50 mg., i.m., weekly for twelve weeks. Children: 2-13 years—25 mg., i.m., every 2 to 4 weeks. Infants: half children's dose.

1. Osol, A. and Farrar, G. E., Jr.: The Dispensatory of the U.S.A., ed. 25, J. B. Lippincott, Phila., 1955, p. 1392.
2. Best, C. H. and Taylor, N. B.: The Physiologic Basis of Medical Practice, ed. 7, The Williams and Wilkins Co., Balt., 1961, p. 1104.

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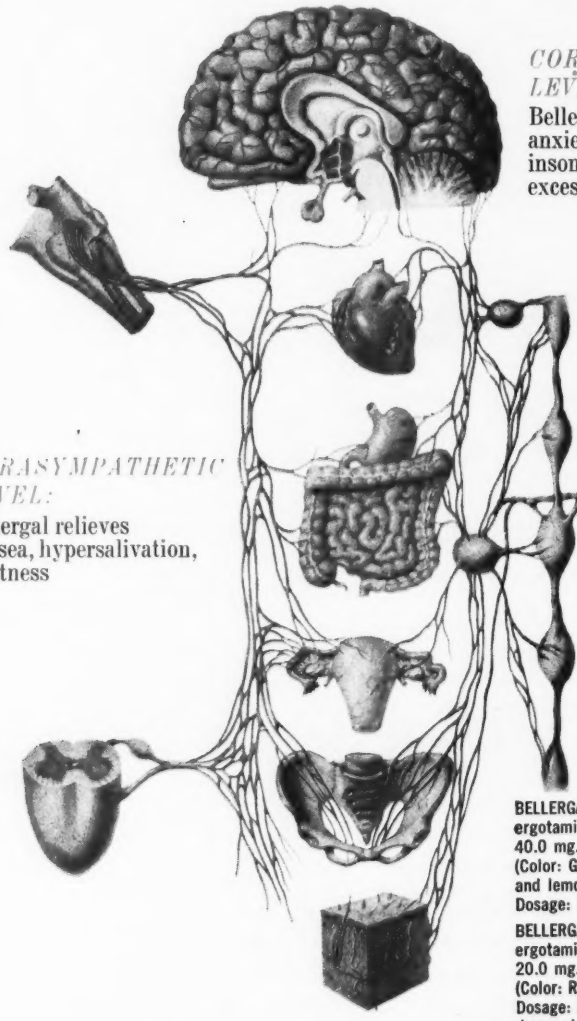

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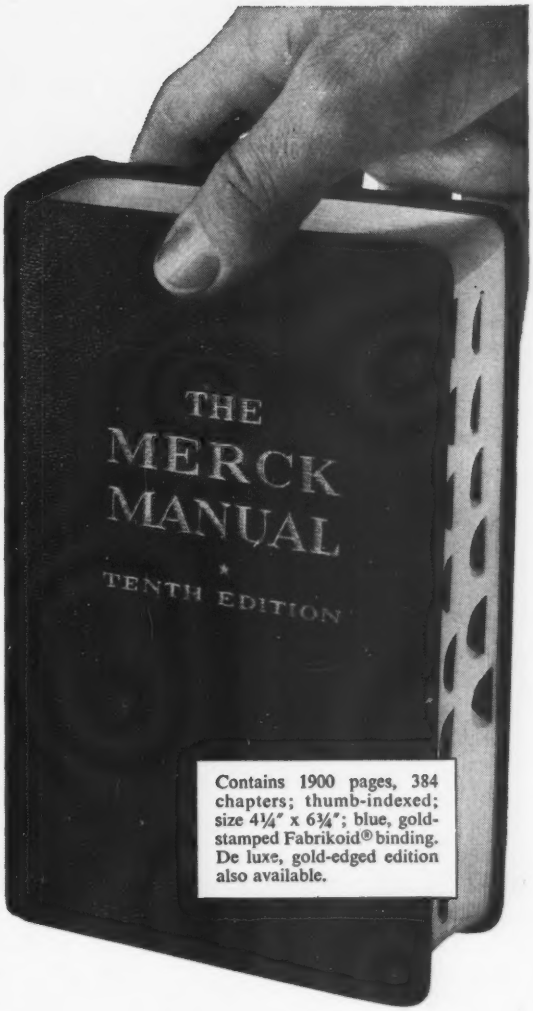

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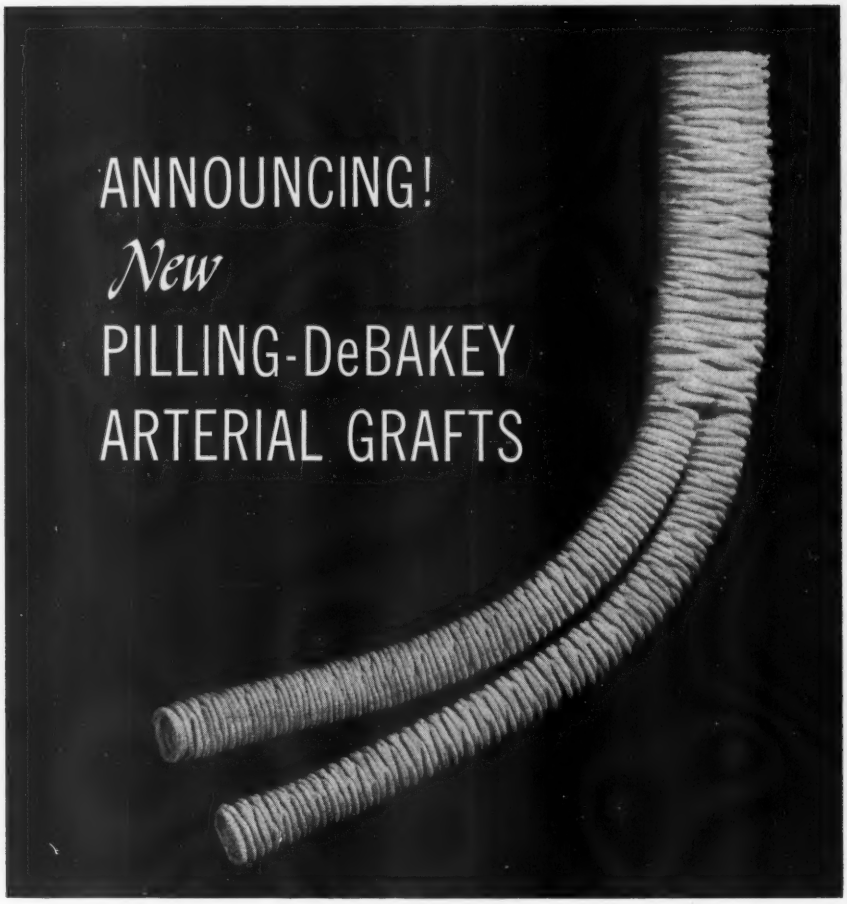

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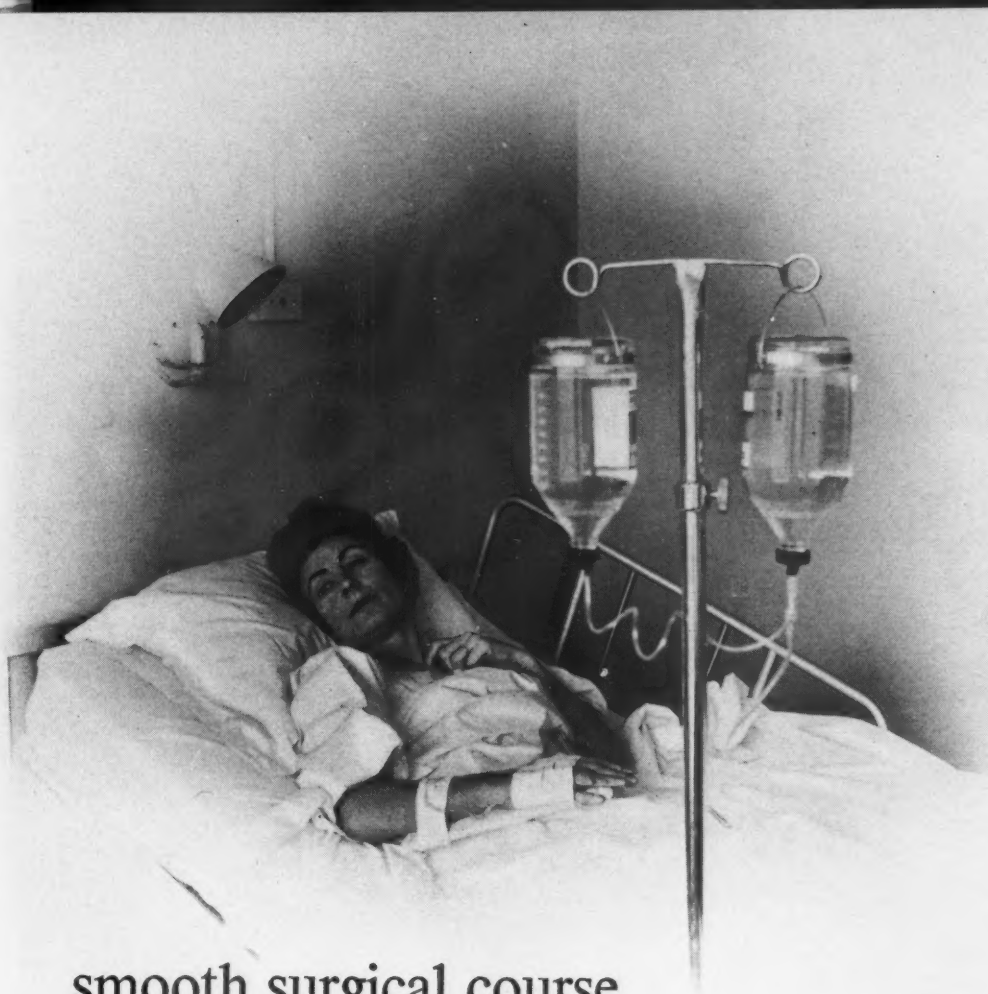

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affirms that Staphcillin is free from such toxic hazards as hearing impairment, renal damage, and blood dyscrasias characteristic of other antibiotics active against resistant staphylococci[1-6,9-14]

STAPHCILLIN...EFFECTIVE IN LIFE-THREATENING INFECTIONS CAUSED BY RESISTANT STAPHYLOCOCCI

Endocarditis, Septicemia, and Osteomyelitis

A 10-year-old boy was admitted to the hospital on August 11, 1960, acutely ill with high fever, and severe pain and swelling of the right knee, right thigh, and right elbow. Six days before, he had injured his right knee. On admission he had a systolic murmur. A short time later cardiac enlargement, slurring of speech, and ataxia of the right arm and leg developed. Blood culture revealed an abundant growth of coagulase-positive staphylococci; the same organisms were later identified in material drained from a large abscess surrounding part of the right femur, which was denuded of periosteum. The diagnosis was acute osteomyelitis, septicemia, and endocarditis caused by staphylococcal infection.

Over a period of 7 weeks, the following antibiotics were administered, but were discontinued because of inadequate improvement or toxicity: penicillin G, tetracycline, chloramphenicol, kanamycin, vancomycin, novobiocin, erythromycin, and ristocetin. Staphcillin was started on Sept. 29, 1960, 1 Gm. I.M., q. 6 h. (later reduced to 3 Gm. daily), and was given for 54 days. Shortly following initiation of this therapy, he became afebrile, and there was marked clinical improvement thereafter. There were no side effects from Staphcillin. As of March, 1961, he had had no recurrence of the infection, was afebrile, had gained weight and the ataxia and speech defect had almost disappeared. There was residual heart murmur. There were signs of osteomyelitis in the right femur on X-ray examination.

Evans, W. E.: Report to Dept. of Clin. Invest., Bristol Laboratories.

Empyema and Concurrent Pseudomonas Wound Infection

A 61-year-old male was injured in an automobile accident. He was operated upon for lacerations of the spleen, left diaphragm, pericardium, and left ventricle. He later developed a *Staph. aureus* empyema and a *Pseudomonas aeruginosa* abdominal wound infection. Chloramphenicol, erythromycin, and penicillin G were given, but discontinued because of inefficacy. Staphcillin was then administered, 2 Gm. q.i.d., for 30 days. Polymyxin B was administered concurrently for the Pseudomonas infection. The condition was improved, with apparent elimination of all infecting bacteria.

Hewitt, W. L.: Report to Dept. of Clin. Invest., Bristol Laboratories.

Pneumonia following Laparotomy

A 37-year-old man had a laparotomy performed at which acute pancreatitis was found. Postoperatively, he developed a bilateral staphylococcal bronchopneumonia. The organism was resistant to penicillin G. Before the laboratory tests were reported, he had been given massive doses of penicillin G for three days with no temperature response. Staphcillin was given intravenously, 1 Gm. every four hours, after which his temperature became normal in 48 hours, "and his clinical response was most gratifying."

Branch, A.; Rodger, K. C.; Lee, R. W., and Power, E. E.: Canad. M. A. J. 83:991 (Nov. 5) 1960.

Enterocolitis after Abdominal Surgery

A 65-year-old woman had profuse watery diarrhea 3 days after an abdominal operation. She became acutely ill, with a temperature of 103°F., tachycardia, leukocytosis, and fluid and electrolyte loss. Staphylococci in pure culture were identified on stool smear and culture. Tetracycline, which she had been receiving since operation, was discontinued, and Staphcillin (1.5 Gm. every 6 hours) administered parenterally. Within 48 hours she was afebrile, and the diarrhea had subsided. Staphylococci were eliminated from the stool. She received Staphcillin for 8 days, and was discharged as well on the 11th postoperative day.

Rutenburg, A. M.; Greenberg, H. L., and Schweinburg, F. B.: New Eng. J. Med. 263:1174 (Dec. 8) 1960.

STAPHCILLIN...EFFECTIVE IN SKIN, SOFT TISSUE AND BONE INFECTIONS CAUSED BY RESISTANT STAPHYLOCOCCI

Persistent Multiple Boils

A 58-year-old male, who for many weeks had suffered from multiple boils from which resistant staphylococci were isolated, was treated for 3 days with sodium methicillin, 1 Gm., q. 4 h., followed by 1 Gm. q. 6 h. for another 3 days. Previous treatment with chloramphenicol and erythromycin had been unsuccessful. At the end of the 6-day period there was complete resolution of all the boils, and the patient was discharged from the hospital. There has been no recurrence.

Knudsen, E. T., and Rolinson, G. N.: Brit. M. J. II:700 (Sept.) 1960.

Cellulitis and Abscess

A 22-year-old male was treated for cellulitis and purulent abscess of the left thigh, resulting from a wound. *Staph. aureus*, resistant to penicillin G, was isolated from the wound tissue. Penicillin G, tetracycline, and erythromycin proved ineffective. Staphcillin was then administered for 17 days, 1 Gm., 5 times daily. The elimination of the infective organisms was impressive.

Bunn, P. A.: Report to Dept. of Clin. Invest., Bristol Laboratories.

Submandibular Abscess

A 24-year-old man was suffering from a submandibular abscess secondary to obstruction and infection in the submandibular duct. This abscess was drained surgically three days before antibiotic therapy, and a heavy growth of coagulase-positive *Staph. aureus* was cultured from the wound. He was given chloramphenicol (to which the organism was reported sensitive) for 7 days, but continued to have a positive culture. Staphcillin was then given intramuscularly for one week. The temperature dropped from 99.6°F. to normal within 24 hours. The drainage soon disappeared. The patient recovered, and was discharged from the hospital two weeks later without any subsequent antibiotic treatment.

Branch, A.; Rodger, K. C.; Lee, R. W., and Power, E. E.: Canad. M. A. J. 83:991 (Nov. 5) 1960.

Osteomyelitis of Femur — Recurrent for 3 Years

A 42-year-old woman had a recurrent osteomyelitis of the left femoral shaft for three years. Upon this admission to the hospital, swelling, heat and tenderness of the thigh were present. Operation revealed a purulent abscess extending into the medullary bone. Cultures showed *Staph. aureus*. The patient was treated with Staphcillin and probenecid for 6 days, following which the drainage became temporarily negative for staphylococci. After an interval of 10 days, a second course of the same treatment was started. Eight days later, the drainage became negative for staphylococci, and subsequently the incisions closed. The patient was treated for a total of 35 days, and was discharged as symptomatically improved. She was readmitted two months later, and was again treated with 8 Gm. of Staphcillin and 1½ Gm. of probenecid per day, for three months, with recovery.

Rifkind, D., and Knight, V.: Report to Dept. of Clin. Invest., Bristol Laboratories.

Retropharyngeal Abscess

A 24-year-old male was treated for a prevertebral, retropharyngeal abscess. The infection was caused by *Staph. aureus*, phage type 80/81. Tetracycline, novobiocin, and vancomycin were only partially effective. Staphcillin was then given I.M., 1 Gm. 6 times per day, for 24 days. The patient was cured. There was a mild local reaction, at the site of injection.

Thompson, R. A.: Report to Dept. of Clin. Invest., Bristol Laboratories.

Multiple Carbuncles and Furunculosis

A 53-year-old male orderly with multiple carbuncles and furuncles, from which staphylococci resistant to penicillin G were cultured, had been followed as an outpatient for five weeks. New lesions occurred in different areas, from which the same organisms were isolated. Staphcillin was given intramuscularly, 1 Gm. q. 6 h., for seven days. Follow-up cultures were negative, and all lesions were closed.

Branch, A.; Rodger, K. C.; Lee, R. W., and Power, E. E.: Canad. M. A. J. 83:991 (Nov. 5) 1960.

STAPHCILLIN THERAPY...

Summary of response in staphylococcal disease

TYPE OF INFECTION	NO. OF PATIENTS	S*	N.C.	I	D
Soft tissue infection	187	158	7	14	8 (2)
Lower-respiratory (pneumonia, empyema bronchitis, lung abscess)	70	49	5	4	12 (3)
Osteomyelitis	54	43	6	4	1 (0)
Septicemia	41	30	3	2	6 (1)
Endocarditis (acute & subacute)	25	22	0	1	2 (0)
Genitourinary	17	14	1	1	1 (0)
Upper respiratory	15	13	2	0	0 (0)
Enterocolitis	12	12	0	0	0 (0)
CNS (abscesses and meningitis)	6	3	1	0	2 (1)
Septic arthritis	6	5	0	0	1 (0)
	433	349	25	26	33 (7)

*[S-satisfactory response; improved or cured] [NC-no change] [I-indeterminate response; not stated or insufficient data] [D-died; ( )-No. of deaths due to infection; other deaths were due to causes such as coronary thrombosis, pulmonary embolism, terminal carcinoma, etc.]

The data in the above table were compiled from published articles and reports to The Department of Clinical Investigation of Bristol Laboratories.

Of the 433 patients included in this summary, 256 received one or more of 21 different antibacterial agents prior to initiation of Staphcillin therapy. Among these patients, 147 received chloramphenicol, 72 received erythromycin, 34 received kanamycin, 28 received novobiocin, 28 received vancomycin.

The two major reasons given for discontinuing other antibiotics were:
1. previous antibiotic was ineffective; 2. previous antibiotic demonstrated toxicity.

SUMMARY OF SENSITIVITY STUDIES

Published data and reports to the Department of Clinical Investigation, Bristol Laboratories, concerning sensitivity of staphylococci to Staphcillin are summarized to date (March, 1961) as follows:

Total number of isolates 8,060

No. of isolates with a Minimum Inhibitory Concentration (M.I.C.) of 6.25 mcg./ml. or less (45 investigators) 8,052

No. of isolates with an M.I.C. of more than 6.25 mcg./ml. (4 investigators: Jevons, Rutenburg, Katz, Eichenwald) 8 (0.09%)

Blood levels well over 12 mcg./ml. are commonly reached for limited periods following the recommended I.M. or I.V. dosage of Staphcillin. Many infections caused by strains with an M.I.C. of 6.25 mcg./ml. have responded well to treatment with the recommended dosage. The rare incidence to date of strains of staphylococci with an M.I.C. of more than 6.25 mcg./ml. is shown in the above summary (0.09% of 8,060 isolates). Only in the future, following treatment of a sufficient number of such cases, can it be known whether they will respond to Staphcillin, and further, what the highest M.I.C. might be that is consistent with good clinical response.

THE ACTIVITY OF STAPHCILLIN IS VIRTUALLY UNAFFECTED BY STAPHYLOCOCCAL PENICILLINASES

The width of the clear zones around the sensitivity discs in Figs. 1 and 2 shows that Staphcillin acts against this resistant strain, and that penicillin G has little or no effect. The similarity in the width of the zones around Staphcillin discs in the light and heavy (increased concentration of penicillinase) inocula shows that penicillinase-producing staphylococci have virtually no effect on the antistaphylococcal activity of Staphcillin.

The clinical effectiveness of Staphcillin against penicillin G-resistant staphylococci is most probably related to Staphcillin's demonstrated resistance to destruction by penicillinase.

Fig. 1
Light Inoculum

Fig. 2
Heavy Inoculum

CONCURRENT ANTIBIOTIC THERAPY IN MIXED OR SUPERINFECTIONS

If mixed or superinfections due to Gram-negative organisms occur during Staphcillin therapy, appropriate measures should be taken. Clinical experience reported to the Department of Clinical Investigation, Bristol Laboratories can be summarized as follows: One or more antibiotics were employed concurrently with Staphcillin in the treatment of 88 patients. Of these, 73 improved, and there was no change in 5. There were 10 deaths, all of which were unrelated to antibiotic therapy; e.g., coronary thrombosis, pulmonary embolism, terminal carcinoma, etc. Among the antibiotics most commonly used with Staphcillin in this series of 88 patients were polymyxin, colistin, bacitracin, streptomycin, kanamycin and chloramphenicol.

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sodium methicillin (sodium dimethoxyphenyl penicillin)

FOR INJECTION

INDICATIONS: Staphcillin is recommended specifically for infections caused by strains of staphylococci susceptible to it and resistant to other penicillins. When laboratory sensitivity tests suggest that the staphylococci involved in an infection are susceptible to Staphcillin and to other antimicrobial agents, selection can be further guided by judgment of the nature of the infection, of the need for bactericidal action, and by considerations of comparative toxicity and convenience of administration.

SUCH INFECTIONS INCLUDE: *Skin and soft tissue infections:* cellulitis, wound infections, carbuncles, pyoderma, furunculosis, lymphangitis and lymphadenitis.

Respiratory infections: staphylococcal lobar pneumonia, bronchopneumonia, or lung abscess combined with indicated surgical treatment.

Other infections: staphylococcal septicemia, bacteremia, acute or subacute endocarditis, acute osteomyelitis and enterocolitis.

Infections due to penicillin-sensitive staphylococci, streptococci, pneumococci or gonococci, should be treated with Syncillin (potassium phenethicillin) or parenteral penicillin G, rather than with Staphcillin. Treponemal infections should be treated with parenteral penicillin G.

DOSAGE AND ADMINISTRATION: *Intramuscularly (deep intragluteal):* Adults – The usual dose is 1 Gm. every 4 to 6 hours. Infants and children – 25 mg. per kg. of body weight (approximately 12 mg. per lb.) every 6 hours.

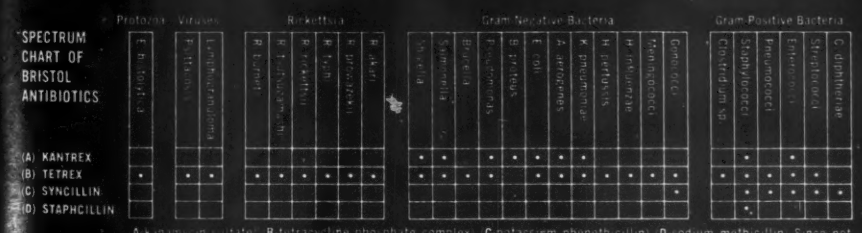
Intravenously: Adults – The usual dose is 1 Gm. every 6 hours, using 50 ml. of sterile saline solution at the rate of 10 ml. per minute.

PRECAUTIONS: Mild skin reactions, e.g., itching, papular eruptions, and erythema have occasionally been observed during treatment and after discontinuance of therapy. Patients with histories of hay fever, asthma, urticaria, and previous sensitivity to any penicillin are more likely to react to all penicillins, and the possibility of anaphylaxis should be kept in mind; epinephrine, antihistamines, and intravenous corticosteroids should be available for emergency treatment. Because of the virtually complete resistance of Staphcillin to destruction by penicillinase, parenteral *B. cereus* penicillinase may not be effective for treatment of allergic reactions. If superinfection by Gram-negative organisms or fungi occurs during Staphcillin therapy, appropriate measures should be taken.

SUPPLY: Staphcillin is available in 1 Gm. dry-filled vials, equivalent to 900 mg. of dimethoxyphenyl penicillin activity.

References: 1. Knox, R.: Brit. M.J. ii:630 (Sept. 3) 1960. 2. Stewart, G. T., *et al.*: Brit. M. J. ii:634 (Sept. 3) 1960. 3. Robinson, G. N., *et al.*: Lancet ii:564 (Sept. 10) 1960. 4. Rutenburg, A. M., *et al.*: New Eng. J. Med. 263:1174 (Dec. 8) 1960. 5. Bunn, P. A., *et al.*: New York J. Med. 60:3074 (Oct. 1) 1960. 6. Branch, A., *et al.*: Canad. M. A. J. 83:991 (Nov. 5) 1960. 7. Gourevitch, A., *et al.*: Paper presented at Conference on Staphcillin in the Therapy of 'Resistant' Staphylococcal Disease, Sept. 7, 1960, State University of New York College of Medicine, Syracuse, New York. 8. Casson, K., and Lannon, J.: *vide supra.* 9. White, A. C., and Varga, D. T.: *vide supra.* 10. Knight, V., and Rifkind, D.: *vide supra.* 11. Douthwaite, A. H., and Trafford, J. A. P.: Brit. M. J. ii:687 (Sept. 3) 1960. 12. Pindell, M. H., *et al.*: *vide supra.* 13. Smith, I. M., and Counts, G. W.: *vide supra.* 14. Hewitt, W. L., *et al.*: *vide supra.*

PROFESSIONAL INFORMATION SERVICE: Whenever you desire additional information concerning clinical experience with Bristol antibiotics, you may avail yourself of the services of the Medical Department of Bristol Laboratories via a collect telephone call to New York, PLaza 7-8520, or by mail to the Medical Department, Bristol Laboratories, 630 Fifth Avenue, New York 20, N.Y.



A-kanamycin sulfate; B-tetracycline phosphate complex; C-potassium phenethicillin; D-sodium methicillin. Since not all strains of the microorganisms listed may be sensitive to a particular antibiotic, clinical therapy should be guided by in vitro antibiotic sensitivity tests whenever possible. *recommended for those staphylococci resistant to other penicillins

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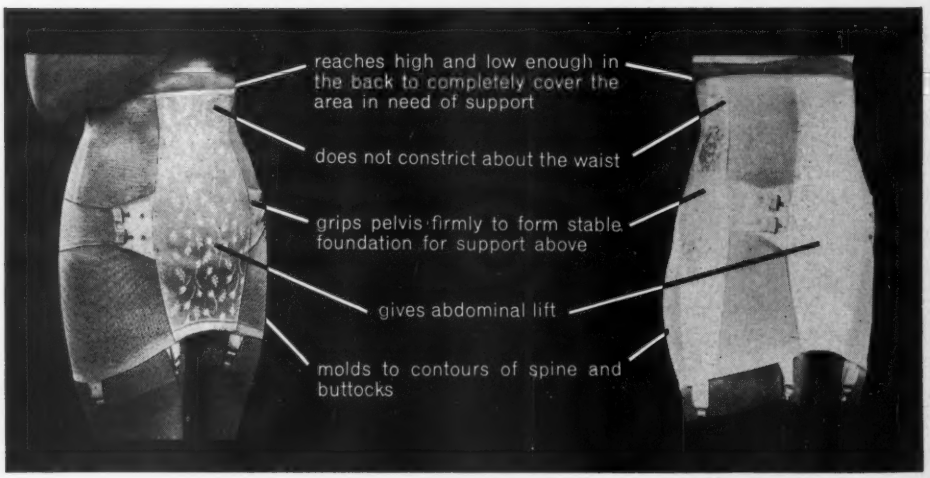
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1. Simeckova, M.; Shaw, W.; Pool, E., and Nichols, E. E.: Numorphan in labor, Obst. & Gynec. 16:119, July, 1960. 2. Snow, D. L., and Sattenspiel, E.: A report on Numorphan in obstetrics, presented at the Congress of the Pan American Medical Association, Mexico City, May, 1960.

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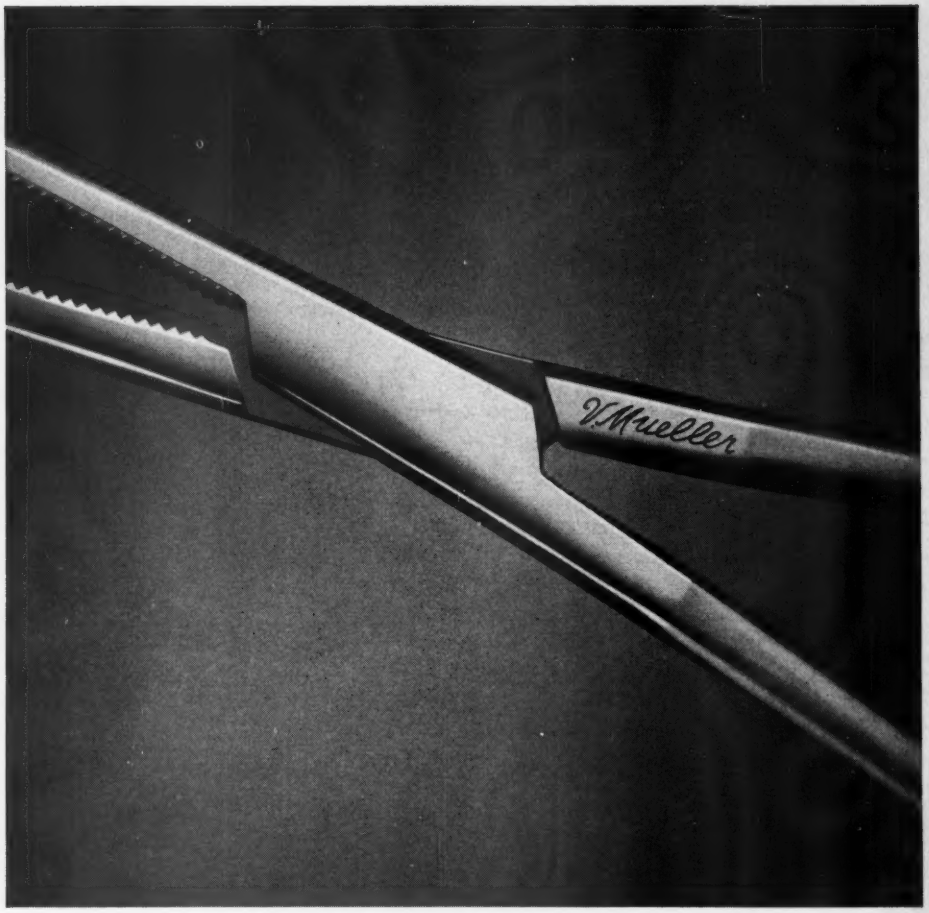

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Available in forms for every need: OXYCEL (oxidized cellulose, Parke-Davis). Pledgets (Cotton-type), 2¼ in. x 1 in. x 1 in.; Pads (Gauze-type) (8-ply), 3 in. x 3 in. and 4 in. x 12 in.; Strips (Gauze-type) (4-ply), 5 in. x ½ in., 18 in. x 2 in., 36 in. x ½ in., and 3 yd. x 2 in.; Foley cones (Gauze-type) (4-ply), 5 in. and 7 in. diameters. Sterile as supplied.

Indications: As an adjunct to effect hemostasis in bleeding associated with capillary oozing. *Use:* Strips—temporary packing of bleeding cavities, nasal passages, and tooth sockets; pads—temporary packing of surgical beds as after biopsies and to cover more or less extensive areas as in laparotomies; pledgets—in neurosurgery and in dental work for small localized bleeding areas; Foley cones—in prostatectomy.

Precaution: Excess amounts should be removed prior to surgical closure to avoid foreign-body reaction. Not to be used in sites of infection or following silver nitrate or other escharotic chemical agents. Contraindicated in clean bone surgery when poor vascularization is present and in instances where rapid callus formation is desired. Should be used sparingly in open reduction of fractures and in cancellous bone. Will not withstand heat sterilization. Remove from container aseptically.

FEB.-1961 (P-568)

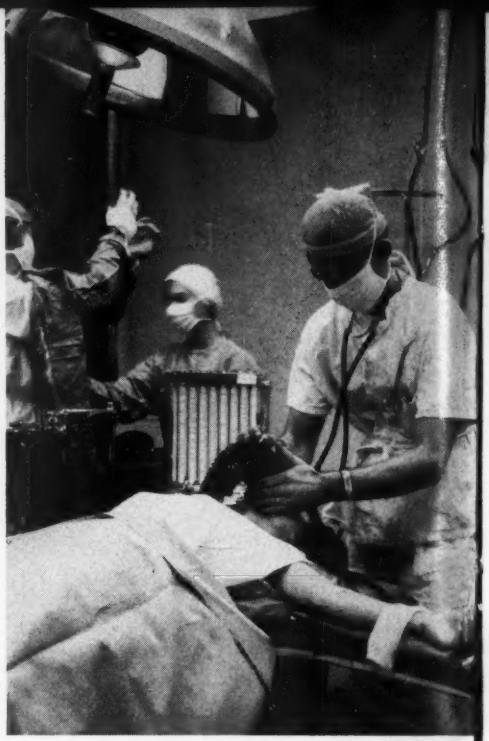
PARKE-DAVIS

PARKE, DAVIS & COMPANY, Detroit 32, Michigan

absorbable hemostatic

OXYCEL®

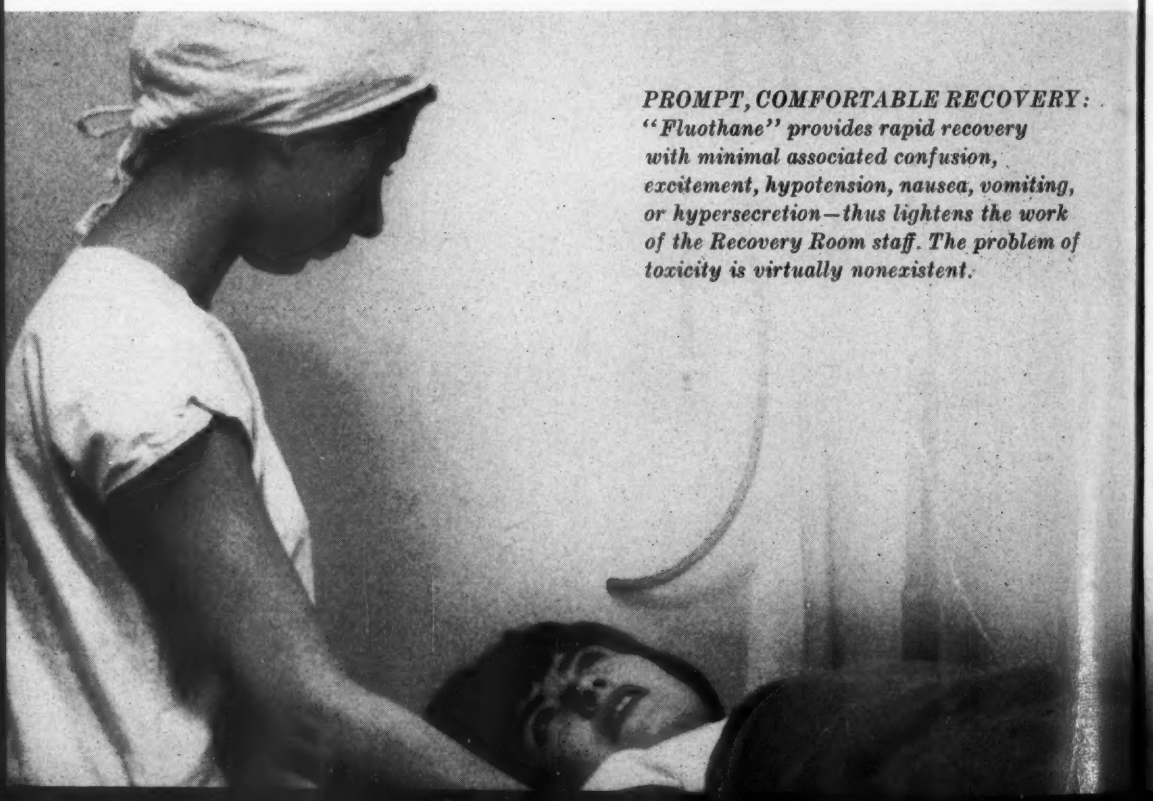
RAPID, SMOOTH INDUCTION:
"Fluothane" anesthesia proceeds from rapid induction into the desired anesthetic plane. The patient quickly goes through Stage II, with few or no signs of excitement.



THE "FLUOTHANE" STORY

AYERST LABORATORIES
New York 16, N. Y.
Montreal, Canada

Ayerst Laboratories make "Fluothane" available in the United States by arrangement with Imperial Chemical Industries, Ltd.



PROMPT, COMFORTABLE RECOVERY:
"Fluothane" provides rapid recovery with minimal associated confusion, excitement, hypotension, nausea, vomiting, or hypersecretion—thus lightens the work of the Recovery Room staff. The problem of toxicity is virtually nonexistent.

PRECISE, EFFECTIVE, RAPIDLY REVERSIBLE ANESTHESIA: The anesthetic plane is easily maintained, easily lightened or deepened. Cardiorespiratory difficulties are rarely encountered, readily corrected. Due to increased flexibility of depth of anesthesia, the surgeon enjoys greater freedom in selecting a specific operative technic.

"Fluothane"®

Brand of Halothane

PRECISION INHALATION ANESTHETIC

Because "Fluothane" is markedly potent, it should be administered by a qualified anesthesiologist who is sufficiently familiar with its characteristics to take the necessary precautions. A vaporizer accurately calibrated to deliver precise concentrations, that may be altered in fractions of 0.1 per cent over a clinical range of 0.5 per cent to 3.5 per cent, should be used. The recommended technics and precautions for administering "Fluothane" are immediately available in the insert accompanying the unit package.

Supplied: No. 3125—Unit package of 125 cc. of Halothane stabilized with 0.01% Thymol (w/w).

NONFLAMMABLE, NON-EXPLOSIVE: "Fluothane" can neither ignite nor explode. Where inhalation anesthesia is indicated, the surgeon is unrestricted in the employment of cautery or X-ray equipment.

6119

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first
first

the first practical answer
to symbiotic therapy of vaginitis
with Döderlein Bacilli...*new*

Dödercil®

Döderlein Bacilli, Wynlit

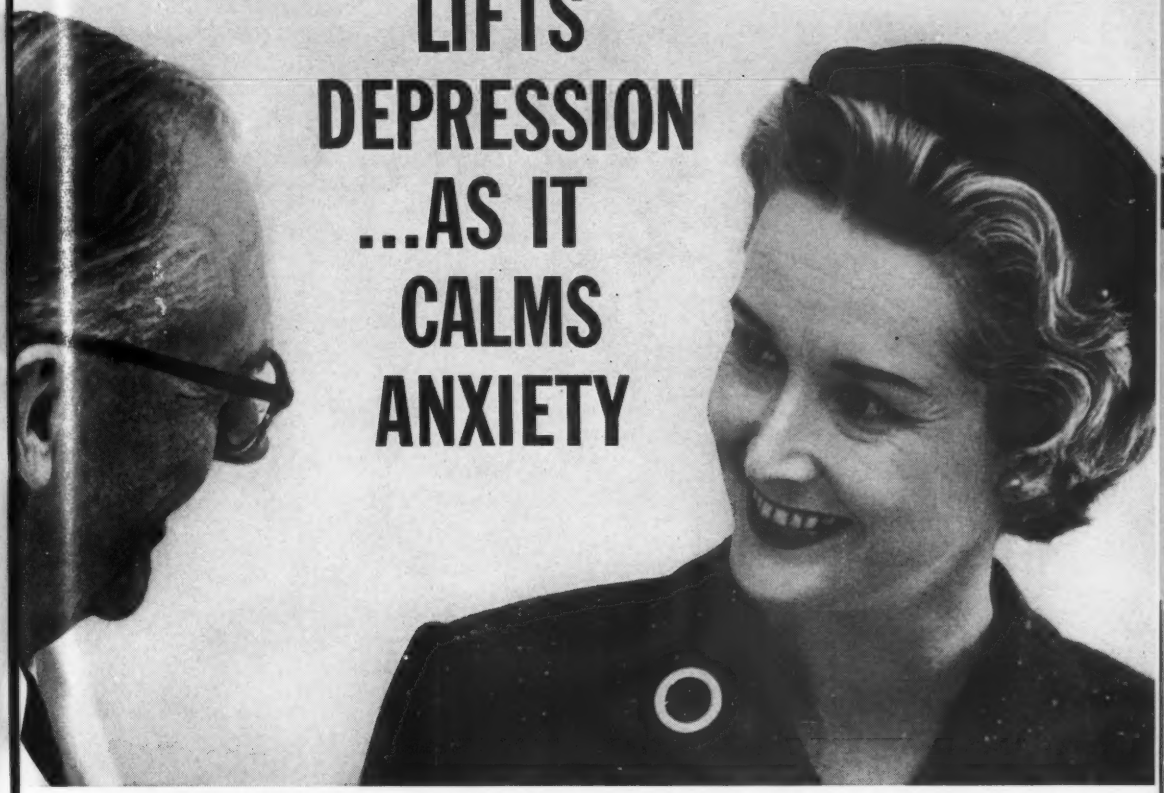
The use of Döderlein Bacilli in the management of vaginitis has been a goal of more than half a century of research; this biological approach to therapy is now available as Dödercil, truly a triumph in research and production.

- **special, pure, dominating strain of viable Döderlein Bacillus with great proclivity for survival**
- **a stable lyophilized powder of assured bacterial count**
- **for vaginal instillation powder is reconstituted as a suspension**
- **a course of vaginal instillations**
  - **—restores normal flora**
  - **—restores normal pH**
  - **—rapidly alleviates symptoms**
  - **—rapidly clears clinical signs**

Orders shipped direct from Madison; literature and prices available upon request.

WYNLIT **WYNLIT PHARMACEUTICALS, INC. Madison, New Jersey**

LIFTS DEPRESSION ...AS IT CALMS ANXIETY



"I feel like my old self again!" Thanks to your balanced Deprol therapy, her depression has lifted and her mood has brightened up – while her anxiety and tension have been calmed down. She sleeps better, eats better, and normal drive and interest have replaced her emotional fatigue.

Brightens up the mood, brings down tension

Deprol's balanced action avoids "seesaw" effects of energizers and amphetamines. While energizers and amphetamines may stimulate the patient – *they often aggravate anxiety and tension.*

And although amphetamine-barbiturate combinations may counteract excessive stimulation – *they often deepen depression and emotional fatigue.*

These "seesaw" effects are avoided with Deprol. It lifts depression as it calms anxiety – a balanced action that brightens up the mood, brings down tension, and relieves insomnia, anorexia and emotional fatigue.

Acts rapidly – you see improvement in a few days. Unlike the delayed action of most other antidepressant drugs, which may take two to six weeks to bring results, Deprol relieves the patient quickly – *often within a few days.* Thus, the expense to the patient of long-term drug therapy can be avoided.

Acts safely – no danger of liver or blood damage. Deprol does not cause liver toxicity, anemia, hypotension, psychotic reactions or changes in sexual function – frequently reported with other drugs.

▲Deprol▲®

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.
Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.
Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.

DD-4024 WALLACE LABORATORIES / *Cranbury, N. J.*

ILOPAN®

to prevent...to relieve... post-op distention and ileus

Surgical stress appears to increase the body's pantothenic acid requirements. ILOPAN (d-pantothenyl alcohol, W-T) provides additional pantothenic acid to aid restoration of normal peristalsis. Clinical studies and hundreds of case histories[1, 2] attest the effectiveness of ILOPAN against postoperative retention of flatus and feces — even paralytic ileus — and in reducing the need for intestinal intubation, or the period of intubation.

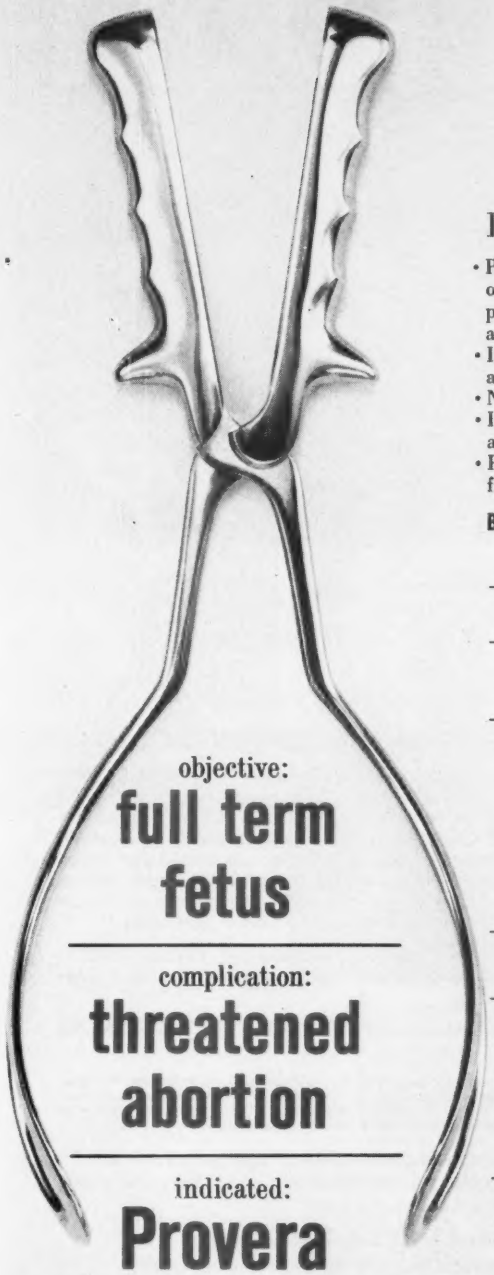
ILOPAN may be used with a high degree of safety — is not contraindicated even under conditions of mechanical bowel obstructions, produces no hyper-peristalsis or cramping, no side effects — and can be routinely administered by the nurse.

Supplied in:
1 cc. AMPULS (250 mg.)
2 cc. AMPULS (500 mg.)
10 cc. VIALS (2500 mg.)

1. Kareha, L. G., de Quevedo, N. G., Tighe, P., Kehrli, H. J., "Evaluation of Ilopan in Postoperative Abdominal Distention," Western J. Surg. Obs. & Gyn., 66:220, 1958.
2. Stone, M. L., Schlussel, S., Silberman, E., Mersheimer, W. L., "The Prophylaxis and Treatment of Postpartum and Postoperative Ileus with Pantothenyl Alcohol," Amer. J. Surgery, 97:191, 1959.

THE WARREN-TEED PRODUCTS COMPANY
COLUMBUS 8, OHIO
Dallas Chattanooga Los Angeles Portland

WARREN-TEED PHARMACEUTICALS®



objective:

full term fetus

complication:

threatened abortion

indicated:

Provera

Upjohn

Here are five reasons why:

- Provera is the only commercially-available oral progestational agent that will maintain pregnancy in critical tests in ovariectomized animals.
- It is four times as potent (by castrate assay) as any other progestational agent.
- No significant side effects have been encountered.
- It is available for both oral and parenteral administration
- Provera gives the economy of effective action from small doses.

Brief Basic Information

	Oral Provera*	I.M. Depo-Provera*☆
Description	Upjohn brand of medroxyprogesterone acetate.	Aqueous suspension, 50 mg. Provera per cc., for intramuscular injection only.
Indications	Threatened and habitual abortion, infertility, dysmenorrhea, secondary amenorrhea, premenstrual tension, functional uterine bleeding.	Threatened and habitual abortion, endometriosis.
Dosage Threatened abortion	10 to 30 mg. daily until acute symptoms subside.	50 mg. I. M. daily while symptoms are present, followed by 50 mg. weekly through 1st trimester, or until fetal viability is evident.
Habitual abortion		
1st trim.	10 mg. daily.	50 mg. I.M. weekly.
2nd trim.	20 mg. daily.	100 mg. I.M. q. 2 wks.
3rd trim.	40 mg. daily, through 8th month.	100 mg. I.M. q. 2 wks. through 8th month.
Supplied:	2.5 mg. scored, pink tablets, bottles of 25; 10 mg. scored, white tablets, bottles of 25 and 100.	Sterile aqueous suspension for intramuscular use only, 50 mg. per cc., in 1 cc. and 5 cc. vials.†

Precautions: Clinically, Provera is well tolerated. No significant untoward effects have been reported. Animal studies show that Provera possesses adrenocorticoid-like activity. While such adrenocorticoid action has not been observed in human subjects, patients receiving large doses of Provera continuously for prolonged periods should be observed closely. Likewise, large doses of Provera have been found to produce some instances of female fetal masculinization in animals. Although this has not occurred in human beings, the possibility of such an effect, particularly with large doses over a long period of time, should be considered.

Provera, administered alone or in combination with estrogens, should not be employed in patients with abnormal uterine bleeding until a definite diagnosis has been established and the possibility of genital malignancy has been eliminated.

†Each cc. of Depo-Provera contains: Medroxyprogesterone acetate, 50 mg.; Polyethylene glycol 4000, 28.8 mg.; Polysorbate 80, 1.92 mg.; Sodium chloride, 8.65 mg.; Methylparaben, 1.73 mg.; Propylparaben, 0.19 mg.; Water for injection, q.s.

The Upjohn Company, Kalamazoo, Michigan

*TRADEMARK, REG. U.S. PAT. OFF. ☆TRADEMARK

"... There is no question that the predictability of satisfactory control of a painful state is high and that the occurrence of untoward reactions is low."[1]

Analexin "... satisfies the majority of the criteria demanded of a moderately potent non-specific analgesic agent."[1] Its range of analgesia is comparable to codeine, yet Analexin is non-narcotic and not narcotic related, and there is no evidence suggestive of tolerance or cumulative toxicity.[1-8] Thus, postoperative administration of Analexin does not induce such undesirable narcotic consequences as nausea, mental depression or habituation, nor will Analexin exert a depressing effect on the respiratory center. And while Analexin produces skeletal muscle relaxation, it has no influence on smooth muscles and therefore will not interfere with resumption of normal peristalsis.

Now postsurgical patients can obtain simultaneous pain relief and muscle relaxation with Analexin . . . a single drug possessing both analgesic and muscle relaxant properties in one molecular structure.[2-4]

Why not prescribe Analexin first for postoperative pain relief? It may prove to be the analgesic of choice.

1. Batterman, R. C.: Ann. New York Acad. Sc. *86*:203, 1960. 2. O'Dell, T. B.: Ann. New York Acad. Sc. *86*:191, 1960. 3. O'Dell, T. B., *et al.*: J. Pharmacol. & Exper. Therap. *128*:65, 1960. 4. O'Dell, T. B., *et al.*: Fed. Proc. *18*:1694, 1959. 5. Gray, A. P., *et al.*: J. Am. Chem. Soc. *81*:4347, 1959. 6. Wainer, A. S.: Ann. New York Acad. Sc. *86*:250, 1960. 7. Clinical data from the files of the Medical Dept., Irwin, Neisler & Co., 1959. 8. Batterman, R. C., *et al.*: Am. J. Med. Sc. *238*:315, 1959.

Analexin®—*for relief of pain.* Each tablet contains 200 mg. phenyramidol HCl.
DOSAGE: Generally 2 tablets at onset of pain, followed by 1 or 2 tablets at intervals of 1 to 4 hours, as needed.

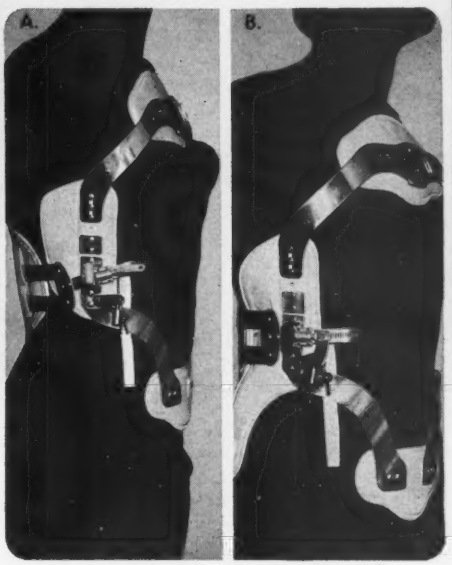
Analexin-AF®—*for relief of pain complicated by inflammatory processes.*
Each tablet contains 100 mg. phenyramidol HCl and 300 mg. aluminum aspirin.
DOSAGE: Generally 2 tablets at onset of pain, followed by 1 or 2 tablets at intervals of 1 to 4 hours, as needed.

IRWIN, NEISLER & CO. **DECATUR, ILLINOIS**

THE JEWETT HYPEREXTENSION BACK BRACE*

FOR

1. Uncomplicated Compression Fractures and/or Kummell's Disease
2. Osteoporosis, with or without compression fractures
3. Marie Strumpell's Arthritis of the spine
4. Adolescent Epiphysitis (Scheurmann's Disease)



A. Standard Hyperextension Model
B. The Post Lumbo-Sacral Fusion Model

RIGID — ADJUSTABLE — LIGHT WEIGHT — WASHABLE

You are also invited to inquire about:

- The EXTENSION-FLEXION Collar
- The MYO-VENT Collar
- The CER-VENT Collar (Extension & Flexion Models)
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Now you can monitor 2 events at once
. . . display a third on a panel meter . . .
change amplifiers as phenomena require

with this single compact, economical SANBORN DUAL MONITOR
specially designed for operating and recovery rooms

This new Sanborn 2-channel visual monitoring system is specifically designed for both large and small hospital use, where an easily operated, dependable and yet economical instrument is needed for 2-channel display of dynamic phenomena such as ECG, EEG, and blood pressure during or after surgery. Compact (12″ x 13½″ x 21″) and completely self-contained, the Model 762 Dual Monitor presents two sharp, clear traces simultaneously on a long-persistence 5″ cathode ray tube, with simple controls for sweep speed, screen scale illumination, brightness, and focus.

Your choice of *interchangeable, plug-in preamplifiers* equip the Dual Monitor for the phenomena to be displayed: ECG, EEG, and pressure types for 'scope display of dynamic events . . . Low Level and Carrier types for presentation of temperature, mean blood pressure, and other slowly changing events on a large scale, external "760" Monitor Meter unit available as an accessory. Also a cardiotachometer (760-3) can be used for indicating heart rate on the "760" Monitor Meter.

Safety in the presence of explosive gases is the reason all "760" preamplifiers are transistorized, low voltage units. The power supply has both current and voltage limiting circuits — eliminating the possibility of high voltage or current coming *from* the preamplifier *to the patient.* Installing the Dual Monitor five feet above floor level then affords complete protection.

Write for complete information on the versatile Model 762 Dual Monitor, interchangeable Preamplifiers, optional Amplifier-Meter unit and Recording Systems for use with it. Address inquiry to Manager, Research Instrument Sales.

MEDICAL DIVISION
SANBORN COMPANY
175 Wyman St., Waltham 54, Massachusetts

Xylocaine®Jelly, BRAND OF LIDOCAINE topical anesthetic, brings fast and long lasting relief and relaxation during painful cystoscopy, sounding, and catheterization. Its water-soluble base adheres to the urinary mucosa; it is nonstaining, nonirritating, nonsensitizing. Xylocaine Jelly lubricates as well as anesthetizes to facilitate instrumentation.

Composition: Xylocaine Jelly contains 2% Xylocaine hydrochloride in a sterile, aqueous vehicle of suitable viscosity.
Dose: 5 cc. to 30 cc. is applied topically, depending on the procedure. Available in 30 cc. collapsible tubes.
Astra Pharmaceutical Products, Inc., Worcester 6, Massachusetts, U.S.A. *U.S. Pat. No. 2,441,498. Made in U.S.A.

ASTRA

NOW... with a single tablet
CONTROL PRENATAL WEIGHT GAIN AND PROVIDE FULL NUTRITIONAL SUPPORT...
with no undesirable CNS stimulation and no pressor effects

NEW NATOREXIC

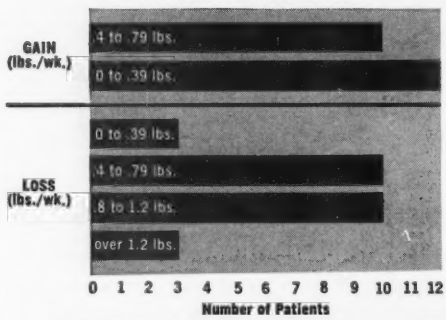
diethylpropion with vitamins-minerals Walker

KEEPS APPETITE IN CHECK, NUTRITION IN BALANCE

Specifically designed for the pregnant patient: Natorexic combines the highly effective anorexic, diethylpropion, with a comprehensive prenatal vitamin-mineral supplement. Just one tablet t.i.d. supplies "...all of the vitamins and minerals commonly recommended for a normal, healthy, comfortable pregnancy ...but markedly reduces the tendency of the patient to overeat."[1]

Effectively controls weight gain...or loss: Natorexic controls the rate of weight increase in the pregnant patient who gains too fast. It also permits loss of excess weight in the "already overweight" pregnant woman. In a series of 50 gravid patients, Jordan[2] obtained the following results with Natorexic therapy:

WEIGHT GAIN OR LOSS DURING PREGNANCY (50 GRAVIDA—NATOREXIC T.I.D.)



Note: The average length of therapy was 8.6 weeks. Two patients had no weight change. Adapted from Jordan[2]

Safe...for the mother and fetus: "Diethylpropion does not produce central nervous system stimulation, insomnia, or any significant change in the blood pressure or pulse rate...No abnormalities of the rate or rhythm of the fetal heart were noted during the study [50 patients treated]."[2] In another study on 138 gravida, Nulsen reports, "there have been no abnormalities noted among the babies and, therefore, it is apparent that the use of diethylpropion during pregnancy is not harmful to the fetus."[3]

Safe...even for the cardiac/hypertensive: "No acute deleterious effects of the drug [diethylpropion] upon blood pressure, pulse, respiration, or electrocardiogram were noted..."[4] when given intravenously (equivalent to *four times* the oral dose) to 15 nonpregnant patients with cardiovascular disorders.

And Natorexic can be taken in the evening, too, without causing sleeplessness.[1,2,5]

DOSAGE: One tablet t.i.d. taken one hour before meals. If desired, a fourth tablet may be taken mid-evening.

SUPPLY: Bottles of 100 orange, coated tablets. Rx only.

REFERENCES: 1. Nulsen, R. O.: *Curr. Therapeut. Res.* 2:102 (March) 1960. 2. Jordan, M. J.: "Safe and Effective Weight Control in Pregnancy," to be published. 3. Nulsen, R. O.: Personal communication. 4. Alfaro, R. D.; Gracanin, V., and Schlueter, E. A.: *Journal-Lancet*, in press. 5. Spielman, A. D.: *Mich. Acad. Gen. Pract. Symposium*, Detroit, 1959.

WALKER LABORATORIES, INC., MT. VERNON, N.Y.

ANNOUNCING... A POTENT ANTIDEPRESSANT WITH EFFECTIVE ANTI-ANXIETY PROPERTIES...

NEW

ELAVIL®

AMITRIPTYLINE HYDROCHLORIDE

MSD

new...a potent antidepressant with effective anti-anxiety properties

EL

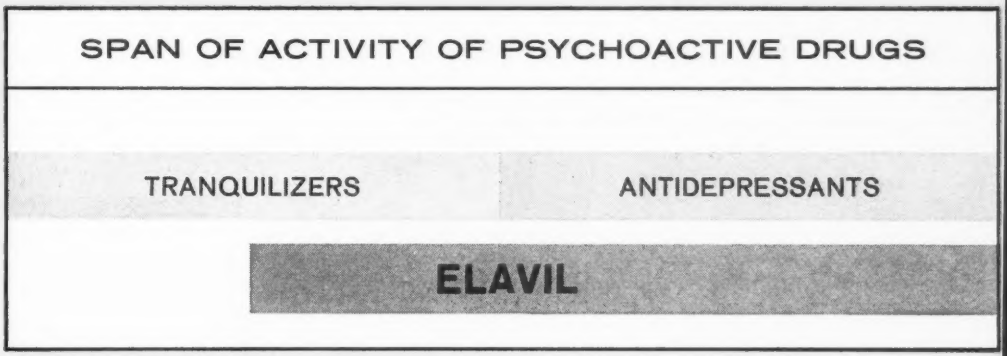
AMITRIPTYLINE HYDROCHLORIDE

RELATIVE UTILITY IN MANAGEMENT OF DEPRESSED PATIENTS

Class of compounds	TARGET SYMPTOMS OF DEPRESSION: *Anxiety*	*Insomnia*	*Depression*	*Over-all relief of symptoms*
TRANQUILIZERS	"Failure of the tranquilizers to produce satisfactory results is due in many cases to their being prescribed for depression, especially depression masked by the more prominent symptoms of anxiety. The underlying depression may be deepened."[1]			+ −
ANTIDEPRESSANTS			"CNS stimulants and anti-depressants, if given to anxious patients, will increase the anxiety...."[1]	+
ELAVIL	"... this drug [ELAVIL] acted both as a tranquilizer and as an anti-depressant..."[2] Many physicians customarily treat anxious or depressed patients with a combination of an antidepressant and a tranquilizer. This is seldom necessary when prescribing ELAVIL because it has both a potent antidepressant and a mild anti-anxiety effect; i.e., it does not exacerbate the symptoms of anxiety in patients with underlying depression as is often the case with other antidepressants.			++

ELAVIL®

effective in patients with depression...
including those with predominant symptoms
of anxiety and tension...provides relief of anxiety
and insomnia associated with depression



INDICATIONS: manic-depressive reaction – depressed phase; involutional melancholia; reactive depression; schizo-affective depressions; neurotic depressive reaction; and these target symptoms: anxiety; depressed mood; insomnia; psychomotor retardation; functional somatic complaints; loss of interest; feelings of guilt; anorexia. May be used whethe the emotional difficulty is a manifestation of neurosis or psychosis,[4] and in ambulatory or hospitalized patients.[3, 4,

USUAL ADULT ORAL DOSAGE: Initial, 25 mg. three times a day, until a satisfactory response is noted. Many patients im prove rapidly, although some depressed patients may require four to six weeks of therapy before obtaining maximum benefit. In severely depressed patients, as much as 150 mg. per day may be given. **Maintenance,** 25 mg. two to four times a day. Some patients may be maintained on 10 mg. four times a day. The natural course of depression is often many months in duration. Accordingly, it is appropriate to continue maintenance therapy for at least three months after the patient has achieved satisfactory improvement in order to lessen the possibility of relapse, which may occur if the patient's depressive cycle is not complete. In the event of relapse, therapy with ELAVIL may be reinstituted.

ELAVIL is not a monoamine oxidase (MAO) inhibitor. No evidence of drug-induced jaundice or agranulocytosis has been noted. Side effects (drowsiness, dizziness, nausea, excitement, hypotension, fine tremor, jitteriness, headache, heartburn, anorexia, increased perspiration, and skin rash), when they occur, are usually mild. However, as with all new therapeutic agents, careful observation of patients is recommended. As with other drugs possessing significant anticholinergic activity, ELAVIL is contraindicated in patients with glaucoma.

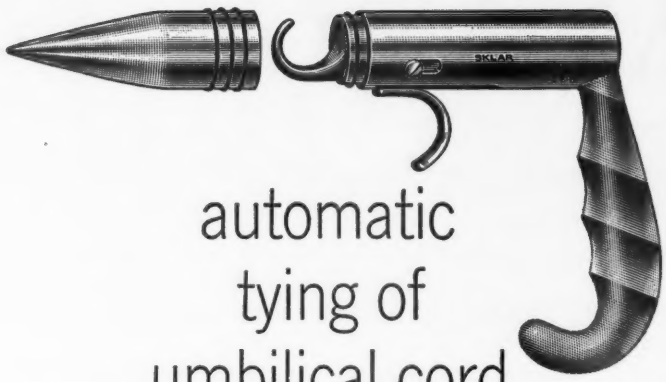
SUPPLY: Tablets, 10 mg. and 25 mg., in bottles of 100. **Injection** (intramuscular), 10 mg. per cc., 10-cc. vials.

REFERENCES: 1. Perloff, M. M., and Levick, L. J.: Clinical Med. 7:2237, Nov. 1960. 2. Freed, H.: Am. J. Psychiat. 117:455, Nov 1960. 3. Dorfman, W.: Psychosomatics 1:153, May-June 1960. 4. Ayd, F. J., Jr.: Psychosomatics 1:320, Nov.-Dec. 1960. 5. Barsa J. A., and Saunders, J. C.: Am. J. Psychiat. 117:739, Feb. 1961.

Before prescribing or administering ELAVIL, the physician should consult the detailed information on use accompanying the package or available on reque

MSD MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.

ELAVIL IS A TRADEMARK OF MERCK & CO., I

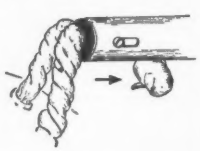


automatic tying of umbilical cord in 20 seconds with the GRAVLEE GUN*

by SKLAR

A Slack cord is looped over hook at desired distance from umbilicus.

B Trigger pull draws cord into barrel.

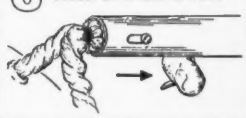


The Gravlee Gun provides a simple, positive, one-hand method for ligating umbilical cords of any size. Assures immediate and permanent hemostasis . . . prevents neonatal stump infections resulting from contaminated tapes or hands. Cords may be stripped if desired. The Gravlee Gun is sterilized by any of the conventional methods.[1]

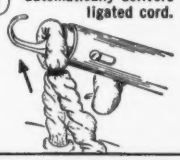
A SKLAR PRODUCT

Write for reprint and descriptive literature:
J. Sklar Manufacturing Co., Long Island City 4, N. Y.

C Additional pull slips sterile rubber band around cord.



D Release of trigger automatically delivers ligated cord.



E Cord is clamped distally and cut in the usual manner.

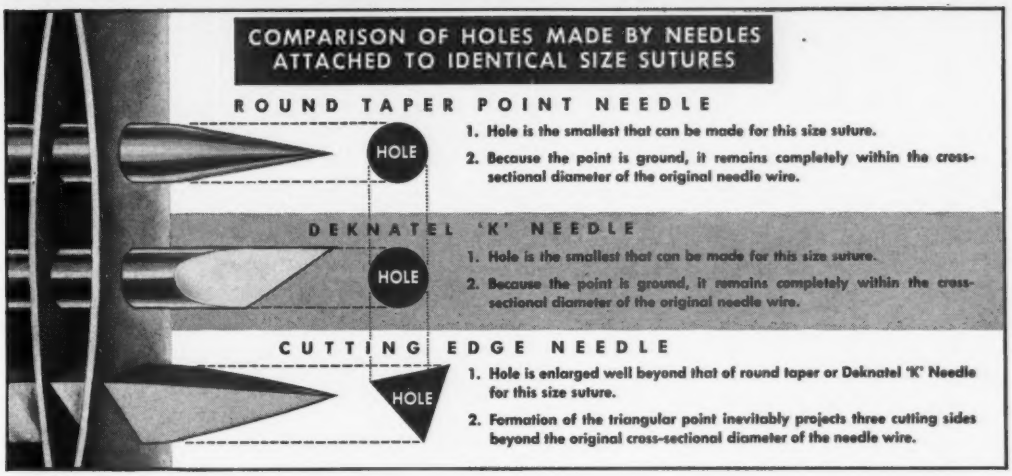
1. Gravlee, L. C., and Jones, W. N.: Obst. & Gynec. 15:43 (Jan.) 1960. * U. S. PAT. NO. 2,942,604.

9 REASONS

WHY THE DEKNATEL 'K' NEEDLE† WILL FACILITATE YOUR GENERAL SURGERY TECHNIQUES.

You will find more.

†U. S. Patent No. 2,869,550


COMPARISON OF HOLES MADE BY NEEDLES ATTACHED TO IDENTICAL SIZE SUTURES
ROUND TAPER POINT NEEDLE
HOLE
1. Hole is the smallest that can be made for this size suture.
2. Because the point is ground, it remains completely within the cross-sectional diameter of the original needle wire.
DEKNATEL 'K' NEEDLE
HOLE
1. Hole is the smallest that can be made for this size suture.
2. Because the point is ground, it remains completely within the cross-sectional diameter of the original needle wire.
CUTTING EDGE NEEDLE
HOLE
1. Hole is enlarged well beyond that of round taper or Deknatel 'K' Needle for this size suture.
2. Formation of the triangular point inevitably projects three cutting sides beyond the original cross-sectional diameter of the needle wire.

❶ UNIQUE DESIGN—NEITHER CUTTING EDGE NOR ROUND TAPER. Sharper than a cutting edge needle, it makes the hole of a round taper point. The Deknatel 'K' Needle point, formed by grinding, remains completely within the diameter of the wire, as illustrated above. There are no lateral projections of cutting blades in any plane to enlarge the hole.

❷ FINEST APPROXIMATION OF WOUNDS. The orientation of its point permits the very edges of wounds to be coapted with ease, producing superior cosmetic results and decreasing the scarring potential.

❸ SAME NEEDLE FOR INTESTINE, PERITONEUM, MUSCLE, FASCIA AND SKIN. The absence of cutting sides on the Deknatel 'K' Needle, its round taper point action and unusual sharpness outmode the need for changing from one type of needle to another. The needle is all purpose.

❹ EXTREMELY FINE PICKUP WITHOUT TEARING OR CUTTING OUT OF TISSUE. The absence of cutting sides and the orientation of its point allow the pickup of finest sections with minimal trauma. Subcuticular layers may be picked up with almost microtome thinness if desired.

❺ CLOSURE OF ABDOMEN OR CHEST IS FASTER. The extraordinary sharpness of the penetrating point makes suturing go faster and more smoothly.

❻ PASSING OF RETENTION SUTURES. It is no longer necessary to "wrestle" a needle through tissue. The sharpness of the Deknatel 'K' Needle gives unusual ease of passage.

❼ FACILITATES SUTURING OF SQUIRMING CHILDREN— "the sharper the needle, the less the pain."

❽ BENDING OF NEEDLES MINIMIZED OR ELIMINATED. The tendency of the Deknatel 'K' Needle to twist, turn or bend is minimal. Because of its sharpness and ease of penetration, the point engages the tissue immediately and surely...advancement is made with minimum effort. Long, uninterrupted sutures may be completed without the needle bending.

❾ NEEDLE HOLDER STABILITY IS MAXIMAL NO MATTER THE ANGLE. Since very little force is needed to advance the point, twisting in the holder is minimized, at whatever angle the needle is held. The excessive force of needle-holder jaws is not, in fact, necessary to stabilize the needle. Any ordinary clamping instrument, such as a hemostat, is adequate.

MAIL THIS COUPON FOR FREE SAMPLES AND LITERATURE

J. A. DEKNATEL & SON, INC.
96-75 222 Street, Queens Village 29, Long Island, N. Y.
Manufacturers of Sutures for Every Operative Procedure

Please send samples of the Deknatel 'K' Needle as follows:

SUTURE:_____ SIZE:_____

NEEDLE: ☐ ⅜ circle ☐ ½ circle ☐ ½ curved ☐ straight

NEEDLE USE: (Specify as "Skin", "General Closure", etc.)

_____

DR._____

ADDRESS_____

CITY_____ ZONE_____ STATE_____

introducing
a new
water-soluble salt
of FURADANTIN

FURADANTIN®
brand of nitrofurantoin
SODIUM

for intravenous use

where parenteral medication is indicated

for treating
urinary tract infections, such as

pyelonephritis, pyelitis, cystitis

for consideration in
systemic bacterial infections

when indicated

(COPY OF PACKAGE INSERT)

FURADANTIN®

brand of nitrofurantoin

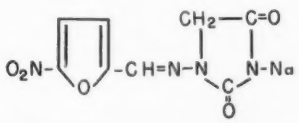
SODIUM

STERILE

For Intravenous Use

ACTIVE INGREDIENT: Each vial contains sufficient material to permit withdrawal of 180 mg. Furadantin, as the sodium salt.

Furadantin Sodium is a synthetic antibacterial agent, one of the antimicrobial nitrofurans, having the following structure:



1-(5-nitrofurfurylideneamino)-hydantoin sodium

INDICATIONS: The antibacterial spectrum of Furadantin encompasses gram-negative organisms such as E. coli, K. pneumoniae and certain strains of Proteus sp., Pseudomonas sp., and Aerobacter sp.; as well as gram-positive organisms such as staphylococci, streptococci, pneumococci, Clostridium sp., B. subtilis.

Furadantin Sodium is indicated in genitourinary infections such as pyelonephritis, pyelitis, cystitis and prostatitis, when the oral form is not feasible. It is also indicated in systemic bacterial infections with the exception of septicemias (bacteremias) unless other therapy has failed or until further work has demonstrated its activity in this condition caused by organisms sensitive in vitro to Furadantin.

In genitourinary tract infections, peroral therapy should replace intravenous when possible. It is not intended to replace surgery when mechanical obstruction or stasis is present.

ADMINISTRATION AND DOSAGE: The crystals must be dissolved just prior to use as follows: Add 15 cc. of 5% Dextrose Injection, U.S.P., or Sterile Water for Injection, U.S.P., to the vial of dry sterile Furadantin Sodium. Empty the syringe forcefully. Shake well to insure complete solution.

FURTHER DILUTION IS REQUIRED
BASED UPON THE PATIENT'S WEIGHT:

Patients weighing over 120 pounds. The recommended dose is 180 mg. of Furadantin in 500 cc. of diluent, twice daily. This is prepared as follows: Withdraw the solution of 180 mg. of Furadantin from the vial and add it to 500 cc. of 5% Dextrose in water, 5% Dextrose in Saline, Normal Saline or 1/6 molar Sodium Lactate intravenous solution. This final solution is to be given by intravenous drip at the usual rate.

Patients weighing under 120 pounds. The recommended dose is 3 mg./lb. of body weight per day divided in two equal doses. This is calculated on the basis that when the Furadantin Sodium in each vial is dissolved in 15 cc. of diluent, each cc. of solution represents 12 mg. of Furadantin. To prepare the final solution, each cc. of the initial Furadantin dilution should be added to a minimum of 33 cc. of parenteral fluid.

CAUTION: In the presence of impairment of renal function or acidosis administer Furadantin Sodium intravenously with caution as with any potent antibacterial agent. If employed under such circumstances the blood pH, CO_2 content or combining power and urea nitrogen or non-protein nitrogen should be followed closely.

The occurrence of a few cases of hemolytic anemia during Furadantin therapy has appeared in the literature.* A small percentage of Negroes and ethnic groups of Mediterranean and Near-Eastern origin has an intrinsic abnormality of the red blood cells. As a result, hemolysis may occur with fava beans and certain drugs, such as primaquine. Thus it is advisable to closely observe such patients receiving Furadantin and to discontinue its administration if there is any indication of this condition developing.

SIDE REACTIONS: If nausea or emesis occur, these may be minimized by slowing the rate of administration, or by decreasing the dosage.

Sensitization occurs rarely in the form of an erythematous, maculopapular cutaneous eruption or urticaria. This is readily controlled by discontinuing treatment.

Occasionally a patient may show minor side reactions such as headache or malaise. No stomatitis, colitis, proctitis, anal pruritus or renal toxicity, have been reported with Furadantin Sodium.

PACKAGING: Sterile 20 cc. vials, containing one adult dose of crystalline sterile Furadantin Sodium (equivalent to 180 mg. of Furadantin).

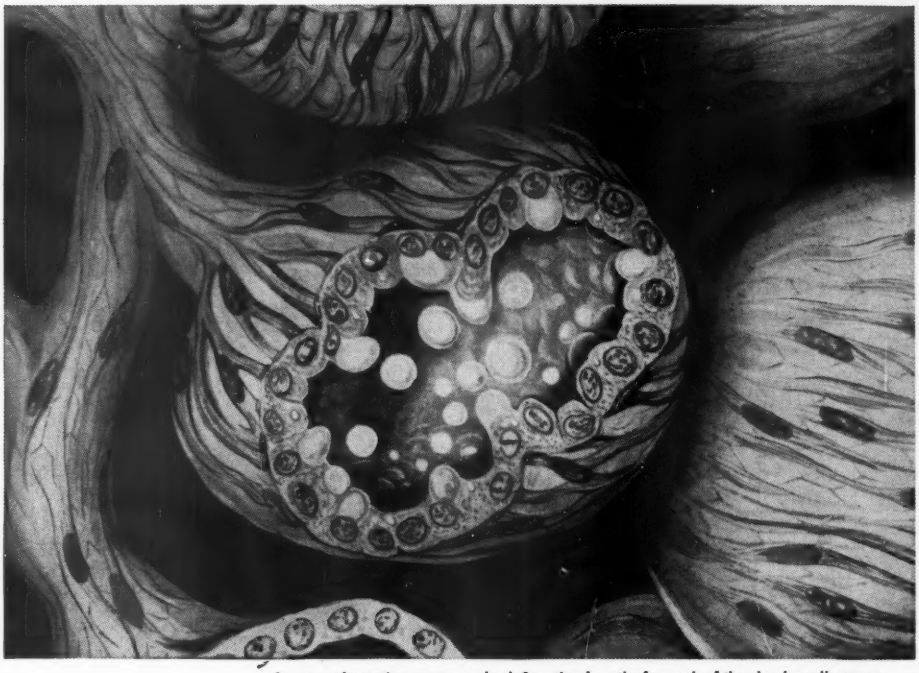
CAUTION: Federal Law prohibits dispensing without prescription.

NOTE: DO NOT ADMINISTER INTRAMUSCULARLY. DO NOT USE WITHOUT DILUTING. MIX JUST PRIOR TO USE.

*West, M., and Zimmerman, H. H.: Hemolytic Anemia in Patient Receiving Nitrofurantoin (Furadantin), J.A.M.A. 162:637 (Oct. 13) 1956. Kimbro, E. L., Jr.; Sachs, M. F.; and Torbert, J. V. Jr.: Mechanism of Hemolytic Anemia Induced by Nitrofurantoin (Furadantin), Fed. Proc. 16:312 (Mar.) 1957.

EATON LABORATORIES
Division of The Norwich Pharmacal Company
NORWICH, NEW YORK

Dec. 1960



Structure of secreting mammary gland. Secretion from the free ends of the alveolar cells passes into the lumen and is ejected by contraction of the myoepithelial cells surrounding the alveoli.

IN SUPPRESSION OF LACTATION

Vallestril®

brand of methallenestril

- gives "excellent" control of lactation
- relieves pain and engorgement
- reduces therapeutic complications

VALLESTRIL, with its major activity in suppressing lactation and lesser action on the endometrium, offers distinct advantages whenever suppression of lactation is indicated or desired.

The lochia is not prolonged.
Normal involution of the uterus is not inhibited.
Reengorgement is uncommon.
Withdrawal bleeding is rare.
Nausea or toxic symptoms are seldom, if ever, attributable to the drug.

These characteristics distinguish Vallestril as a singularly safe and effective estrogenic agent, particularly free from toxicity and post-therapeutic complications.

FOR SUPPRESSION OF LACTATION

The recommended dosage of Vallestril is two 20-mg. tablets daily for five days, begun as soon as possible after delivery. Vallestril is supplied as uncoated, unscored tablets of 20 mg. (and also as uncoated, scored tablets of 3 mg. for the relief of symptoms of the menopause).

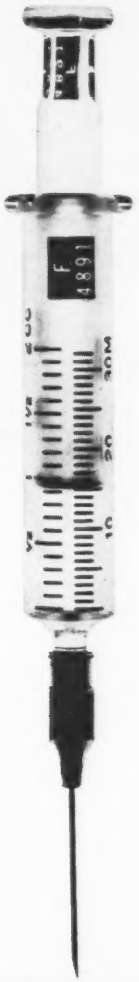
G. D. SEARLE & CO.
CHICAGO 80, ILLINOIS
Research in the Service of Medicine

in local anesthesia

CARBOCAINE®

BRAND OF MEPIVACAINE

"...a noteworthy forward step...."[1]



Quicker anesthesia[2] / longer lasting anesthesia[3] / no epinephrine needed*[4] / virtually no vasodilatation[4] / greater safety[5] "This combination of properties offers the opportunity of obtaining almost instantaneously profound and long-lasting anesthesia, with negligible tissue irritation, and without complicating systemic effects of vasoconstrictors."[1]

References: 1. Sadove, M. S., and Wessinger, O. D.: **J. Internat. Coll. Surgeons** 34:573, Nov., 1960. **2.** Erickson, J. C., III, and Hricko. M. J.: **Guthrie Clin. Bull.** 29:45, 1959. **3.** Gordon, R. A.; Kerr, J. H., and Taylor, Russell: **Canada. Anaesth. Soc. J.** 7:290, July, 1960. **4.** Sadove, M. S.: **New Physician** 9:39, Sept., 1960. **5.** Young, J. A.: **Anesth. & Analg.** 39:451, Sept.-Oct., 1960.

*If desired, epinephrine may be used in infiltration anesthesia for hemostasis.

Winthrop LABORATORIES
New York 18, N. Y.

six sizes
a thousand and one uses

The wide range of sizes of 'Vaseline' Sterile Petrolatum Gauze U.S.P. gives it a thousand and one uses in the hospital and the office treatment room. As a pressure dressing in surgery . . . an occlusive dressing in burns . . . an emollient dressing on dry and nonacute skin lesions . . . a packing in nose, eye, and ear procedures . . . here is a dressing that is convenient to use and of guaranteed, sealed-in sterility.

½" x 72" Selvage-edged Packing
(in disposable plastic tube)
Packing for nose, ear canal, or eye socket; submucous resection, rhinoplasty, ocular evisceration or other surgical intervention, nasal hemorrhage.

1" x 36" Strip
(in heat-sealed foil envelope)
Circumcisions, finger dressings, hand surgery, podiatric applications, small-area burns, pilonidal cysts, small packings.

3" x 9" Strip, and 3" x 3" Pad
(in heat-sealed foil envelope)
Skin grafts, colostomies, small-area wounds — traumatic or surgical.

3" x 18" Strip
(in heat-sealed foil envelope)
Burns, dermabrasion, traumatic wounds, eschar removal, abrasions, compound fractures, amputation stumps, urological and proctological work, and many other surgical procedures p.r.n.

3" x 36" Strip
(in heat-sealed foil envelope)
When a larger dressing is needed for the indications above.

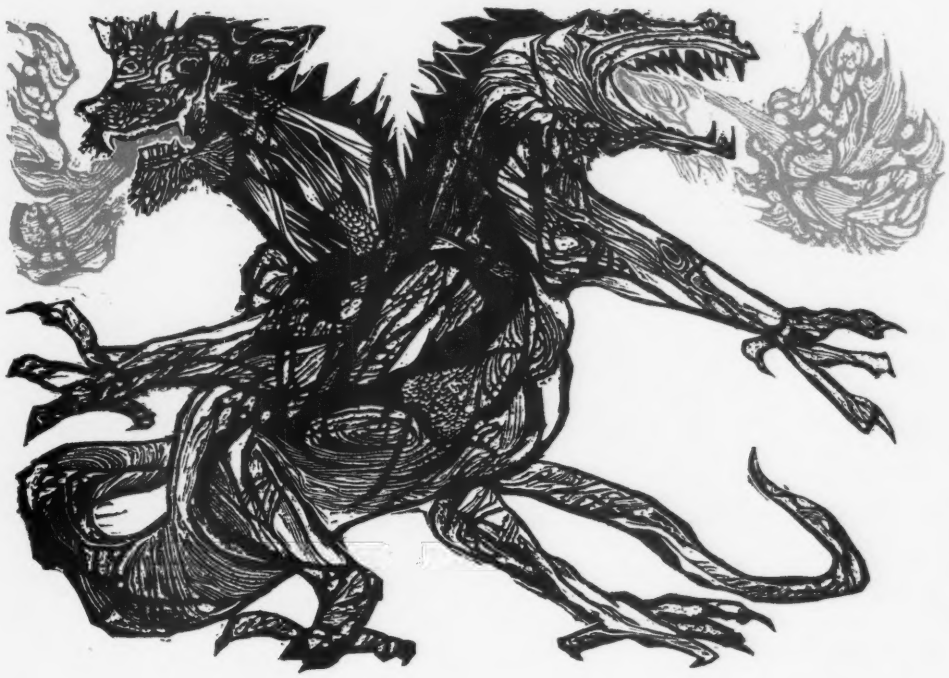
6" x 36" Strip
(in heat-sealed foil envelope)
Extensive burns, pemphigus, cancer resections. large-area wounds.

'Vaseline' Sterile Petrolatum Gauze U.S.P.

Professional Products Division • Chesebrough-Pond's Inc., New York 17, N. Y.

Vaseline® is a registered trademark of Chesebrough-Pond's Inc.

When severe pain accompanies skeletal muscle spasm ease both 'pain & spasm'



with Robaxisal®

Robins

ROBAXIN® with Aspirin

A dual-acting skeletal muscle relaxant-analgesic, combining the clinically proven relaxant action of ROBAXIN with the time-tested pain relieving action of aspirin.

Each ROBAXISAL Tablet contains:
ROBAXIN (methocarbamol Robins) 400 mg. Acetylsalicylic acid (5 gr.)..... 325 mg.
U.S. Pat. No. 2770649
Supply: Bottles of 100 and 500 pink-and-white laminated tablets.

Or ROBAXISAL®-PH (ROBAXIN with Phenaphen®) — when anxiety is associated with painful skeletal muscle spasm.

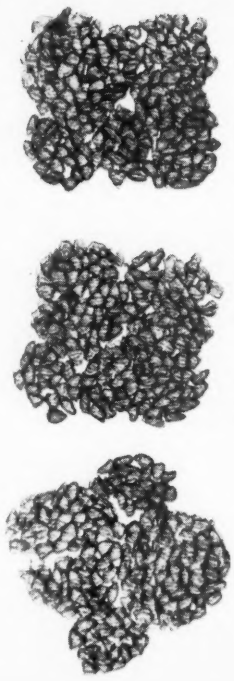
Each ROBAXISAL-PH Tablet contains:
ROBAXIN (methocarbamol Robins) 400 mg. Acetylsalicylic acid ..... 81 mg.
Phenacetin 97 mg. Hyoscyamine sulfate 0.016 mg. Phenobarbital (1/8 gr.) 8.1 mg.
Supply: Bottles of 100 and 500 green-and-white laminated tablets.

A. H. ROBINS CO., INC., Richmond 20, Virginia
Making today's medicines with integrity ... seeking tomorrow's with persistence.

ORDINARY silk suture 5-0

Cross-sections, unretouched microphotograph

Gums and other impurities—comprising 30% of silk—have been removed after braiding. Resulting loss in suture volume causes looseness, limpness and handling difficulties despite the addition of coatings and other additives.



de-gumme
befor
braidin
for ide
handlin
properties

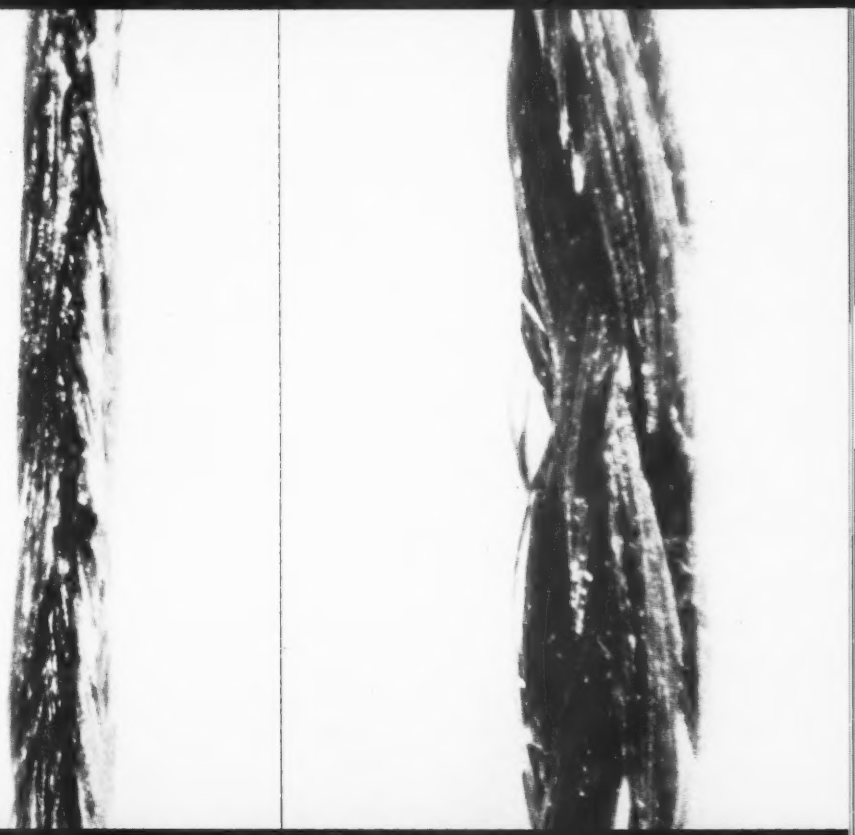
ETHICON PERMA-HAND Surgical Silk Suture 5-0

Cross-sections, unretouched microphotograph

But Ethicon removes gums and impurities **before** braiding. Suture remains tightly braided. And there are no loose strands that cause ends to "broom." Because the handling qualities are permanently built into ETHICON PERMA-HAND Surgical Silk, no special coatings are needed.

not a limp strand...
but a suture with "hand"

PERMA-HAND surgical silk



b ided with
"s w control"...
fo uniform
di meter and
ti htness
o braid

ETHICON PERMA-HAND Surgical Silk Suture 5-0

Unretouched microphotograph

Here, strands are tightly held within the suture because the braid is even throughout. Ethicon "slow-controlled" braiding assures "live" silk that resists breakage during knot-tying.

ORDINARY silk suture 5-0

Unretouched microphotograph

Note typical loose strand and unevenness of the braid. Rapid braiding does not permit adequate control of uniformity... results in "dead" and brittle silk. This causes strand to shear against itself and frequently break during knot-tying.

In a recent national survey, surgeons indicating characteristics most desirable in a surgical silk suture expressed these preferences:

- **uniform strength**
- **optimum extensibility**
- **optimum firmness and maximum pliability**
- **uniform diameter and smoothness**
- **firm knot-holding characteristics**
- **resistance to breakage**

These are the qualities that add up to superior "hand." In ETHICON PERMA-HAND Surgical Silk, they're built into the suture through controlled processing—from raw silk to finished suture. That's why ETHICON PERMA-HAND Surgical Silk was uniformly preferred by these surgeons.

ETHICON®

reverse

hypovolemic shock quickly, economically

without the dangers of blood transfusion

An estimated 3,000 patients die each year as the result of blood transfusion reactions.[1] When hypovolemic shock is treated with ALBUMISOL®, most of the risks inherent in blood transfusion are bypassed. With ALBUMISOL, there is— ■ **no danger of hepatitis** ■ **no waiting or expense for typing, cross-matching, or grouping.**

Most importantly, ALBUMISOL is the protein responsible for 80 per cent of the colloid osmotic pressure of plasma. It therefore fills the most urgent need in hypovolemic shock—restoration of pressure.

ALBUMISOL 25% (salt poor) is also available to help you manage nutritional deficiencies and severe fluid retention of advanced cirrhosis and nephrosis. Increased production now makes possible new lower prices on both products.

Albumisol®

NORMAL SERUM ALBUMIN (HUMAN)

ready for immediate blood volume replacement

SUPPLIED: ALBUMISOL 5% in 250-cc. and 500-cc. bottles.
ALBUMISOL 25% (salt poor) in 20-cc. and 50-cc. bottles.

1. Hirsh, B. D.: Medicolegal Digest, 1:21, June, 1960.

Additional information is available to the physician on request.

ALBUMISOL is a trademark of Merck & Co., Inc.

MSD MERCK SHARP & DOHME
Division of Merck & Co., Inc. • West Point, Pa.

New Bauer & Black hosiery provide therapeutic support . . . plus the high-fashion appeal that assures patient cooperation

For your patients with varicose veins, Bauer & Black introduces a new high-fashion *seamless* hose (a style which over 50% of women prefer).

With these hose, neither you nor your patient need compromise. They have rubber in every supporting strand—the only true way to provide positive, even pressure over the veins (as opposed to the superficial pressure of "support nylons" that do more stretching than supporting). And now your patients have a choice—sheer 51 gauge full-fashioned, or the new sheer *seamless* style.

Prescribe Bauer & Black elastic stockings for your patient with varicosities, and know she'll wear them willingly because of their high-fashioned look. Expert fitting is available at leading drug, department, and surgical stores.

For new reference on the treatment and prevention of varicose veins by compression, write Bauer & Black, Dept. SGO-6, 309 West Jackson Blvd., Chicago 6, Illinois.

BAUER & BLACK

THE KENDALL COMPANY
BAUER & BLACK DIVISION

surgical instruments

Surgical instruments etched "Stille" assure you of the perfection inherent in fine Swedish craftsmanship. Put this perfection in your hands. You will instantly recognize and appreciate the superior heft, feel and balance of genuine Stille instruments.

For further information about Stille stainless steel surgical instruments see your local Ohio Chemical dealer —or write directly to Dept. SGO-6

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OHIO CHEMICAL & SURGICAL EQUIPMENT CO.
Madison 10, Wisconsin
On West Coast: Ohio Chemical Pacific Co.
Berkeley 10, California
(Divisions of Air Reduction Co., Inc.)

meeting a widespread professional demand

BARD-PARKER DISINFECTING SOLUTIONS

B-P HALIMIDE
Concentrate Disinfectant

. . . now **improved,** HALIMIDE disinfectant—**free from objectionable odor,** is a concentrate of low surface tension and excellent penetrating qualities. Perfect for inexpensive instrument disinfection, 1 oz. mixed with 1 gal. of water makes a stable—clear—non-corrosive—non-staining solution. TUBERCULOCIDAL when diluted with alcohol. No anti-rust tablets to add—no need for frequent changing.

B-P CHLOROPHENYL Disinfectant

. . . an ideal instrument disinfecting solution for professional office use. It is **rapid** in destruction of commonly encountered vegetative bacteria—free from phenol (carbolic acid) and mercurials—not injurious to skin or tissue. It is used full strength—has a pleasant odor—its germicidal efficiency is not affected by soap.

B-P FORMALDEHYDE GERMICIDE

. . . sporicidal • tuberculocidal • bactericidal virucidal • fungicidal

it is especially suitable for hospital use in the chemical disinfection of instruments and protection of surgical **sharps.** It is used full strength—and within 5 minutes will **kill** TUBERCLE BACILLI—vegetative pathogens and spore formers—the spores themselves within 3 hours.

B-P **BARD-PARKER COMPANY, INC.**
DANBURY, CONNECTICUT
A DIVISION OF BECTON, DICKINSON AND COMPANY

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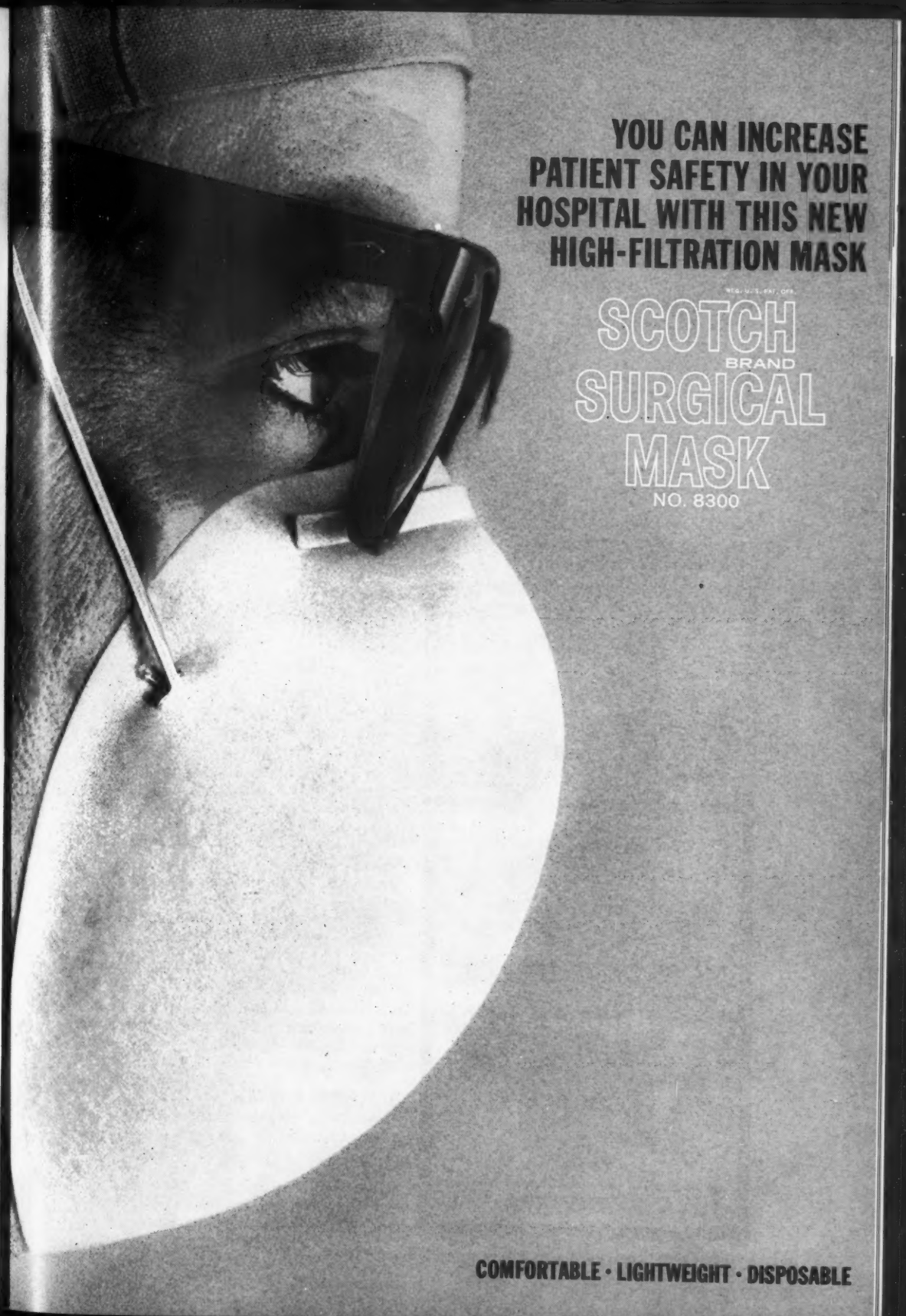

YOU CAN INCREASE
PATIENT SAFETY IN YOUR
HOSPITAL WITH THIS NEW
HIGH-FILTRATION MASK
REG. U.S. PAT. OFF.
SCOTCH
BRAND
SURGICAL
MASK
NO. 8300
COMFORTABLE • LIGHTWEIGHT • DISPOSABLE

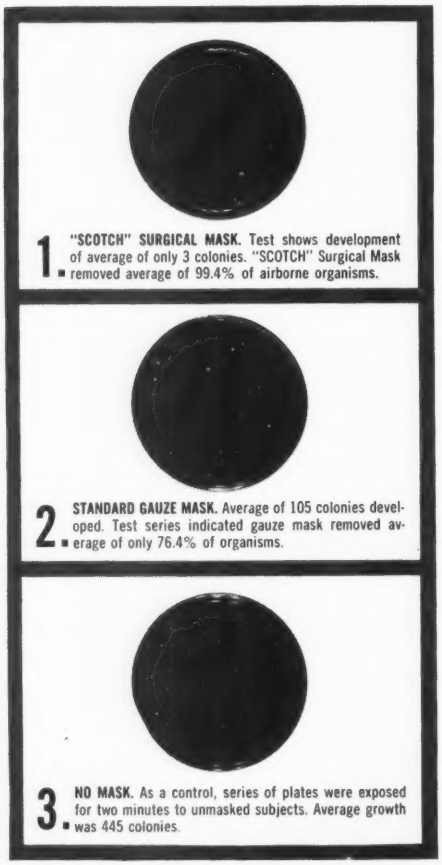
HERE ARE THE FACTS ON THE NEW SCOTCH® BRAND SURGICAL MASK

REG. U.S. PAT. OFF.

HOW DOES THE "SCOTCH" BRAND SURGICAL MASK COMPARE IN FILTERING EFFICIENCY WITH GAUZE MASKS?

In hundreds of controlled comparative tests (utilizing both in-use and mechanical sampling methods ... both new and used masks .. both brief and sustained testing periods) the "SCOTCH" Surgical Mask averaged up to 35 times more effective than gauze in filtering out airborne bacteria.

TYPICAL TEST RESULT: (masked subjects, 2 minute test period)



1. "SCOTCH" SURGICAL MASK. Test shows development of average of only 3 colonies. "SCOTCH" Surgical Mask removed average of 99.4% of airborne organisms.

2. STANDARD GAUZE MASK. Average of 105 colonies developed. Test series indicated gauze mask removed average of only 76.4% of organisms.

3. NO MASK. As a control, series of plates were exposed for two minutes to unmasked subjects. Average growth was 445 colonies.

WHY IS THE DESIGN AND CONSTRUCTION OF THE "SCOTCH" SURGICAL MASK SO EFFICIENT?

The "SCOTCH" Surgical Mask is molded of a new stabilized-porosity synthetic fabric with an unusually high filtration capacity. Unlike soft, woven fabrics such as gauze, its built-in porosity is permanent. There is little or no variation from mask to mask and no radical loss of efficiency due to compression, matting, or wetting during use.

HOW DOES THE CONTOURED SHAPE OF THE MASK INCREASE ITS FILTERING EFFICIENCY?

Because it is held away from the mouth and nostrils, virtually the entire inner surface of the "SCOTCH" Surgical Mask acts as a filter. Exhaled moisture droplets are not propelled through a small area, but are dissipated at low velocity within the mask.

MUST THE "SCOTCH" SURGICAL MASK BE CHANGED DURING PROLONGED PROCEDURES?

Rarely. Whereas gauze masks rapidly lose efficiency due to wetting and must be changed frequently, the "SCOTCH" Surgical Mask shows little or no drop-off in filtering effectiveness in extended use.

HOW IS LEAKAGE AROUND THE MASK EDGES CONTROLLED?

The adjustable nose piece, contour shape and elastic band of the "SCOTCH" Surgical Mask provide a close fit that minimizes air leakage. Fogging of glasses is almost totally eliminated.

DOES THE MASK'S HIGH FILTRATION MAKE BREATHING DIFFICULT?

Not at all. Because of its large effective filtering area, breathing is actually easy. There is no significant CO_2 build-up within the mask. Speech is not muffled.

WHAT ABOUT COMFORT?

The "SCOTCH" Surgical Mask has been called "the most comfortable yet." It is lightweight (9 masks weigh only one ounce). Measured skin temperatures have proved 1° cooler than inside gauze masks. Vision is not obstructed. Elastic band holds mask in correct position without slipping or binding. There are no strings to tie or adjust.

Enthusiastically accepted. The "SCOTCH" Surgical Mask shown in use in a leading midwestern hospital—one of the many institutions that have already standardized on this high-filtration disposable mask.

IS THE "SCOTCH" SURGICAL MASK EXPENSIVE TO USE?

No. An independent six-month cost study at a leading hospital showed virtually identical over-all costs whether the "SCOTCH" Surgical Mask or gauze masks were used. "SCOTCH" Surgical Masks cost approximately 9 cents each at quantity prices . . . eliminate all inspection, laundry and re-sterilization costs.

CAN THE MASK BE AUTOCLAVED?

Yes. While this mask is designed and priced to be fully disposable, it may be steam autoclaved with no loss of filtering efficiency.

HOW CAN YOU TRY THE "SCOTCH" SURGICAL MASK IN YOUR HOSPITAL?

Your surgical supply dealer can fill your trial order promptly—box of 50 masks, only $6.00; case of 10 boxes, $54.00†. Or, for free samples and additional literature, contact your 3M Sales Representative or write to 3M Company, Dept. NAH-61, 900 Bush Avenue, St. Paul 6, Minnesota.

†PRICES SUBJECT TO CHANGE WITHOUT NOTICE.

REG. U. S. PAT. OFF.

SCOTCH BRAND SURGICAL MASK*

NO. 8300

MINNESOTA MINING AND MANUFACTURING COMPANY

...WHERE RESEARCH IS THE KEY TO TOMORROW

3M COMPANY

*PATENT PENDING

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a pair of gynecologic patients:

both are free of pain—but only one is on

DILAUDID®

(Dihydromorphinone HCl)

swift, sure analgesia normally unmarred by nausea and vomiting

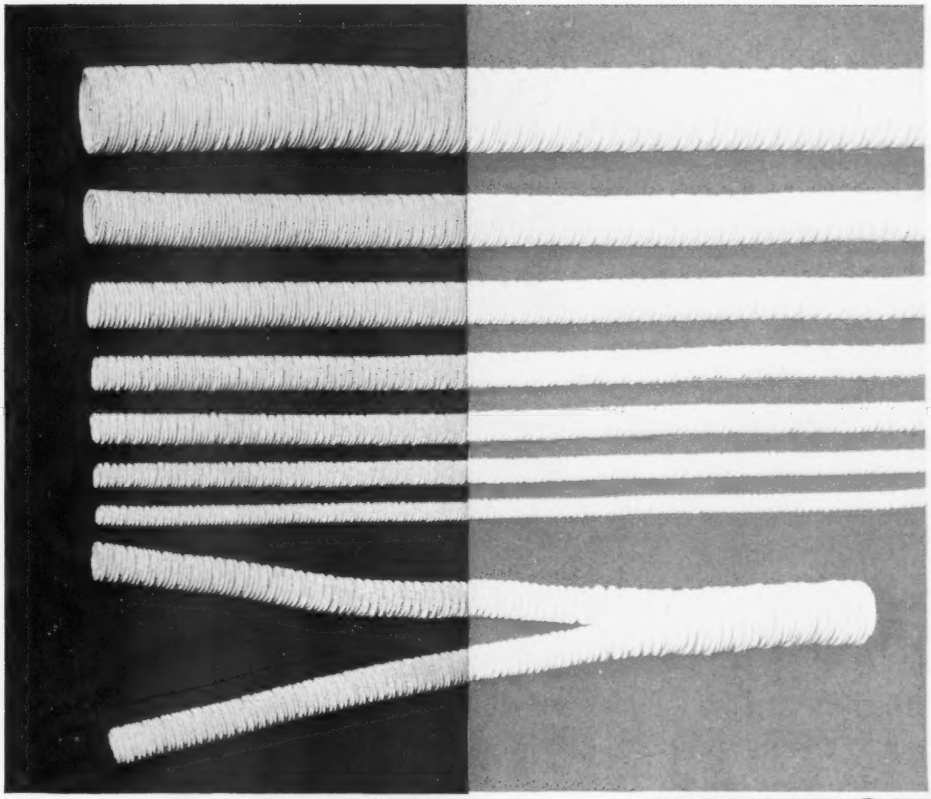
DILAUDID provides unexcelled analgesia before and after gynecologic, obstetric and surgical procedures. Its high therapeutic ratio is commonly reflected by lack of nausea and vomiting — and marked freedom from dizziness, somnolence, anorexia and constipation.

by mouth **by needle** **by rectum**

2 mg., 3 mg., and 4 mg.

May be habit forming—usual precautions should be observed as with other opiate analgesics.

KNOLL PHARMACEUTICAL COMPANY • ORANGE, NEW JERSEY



DeBAKEY™ GRAFTS OF DACRON®

Dacron seamless arterial grafts and aortic bifurcations are made to the precise specifications of Michael E. DeBakey, M.D., and members of the Department of Surgery, Baylor University; by the U.S. Catheter & Instrument Corp.

With these Dacron grafts and our present line of Teflon grafts, C. R. Bard now provides the most comprehensive line of vascular prostheses ever, offering the surgeon one source for the widest range of types and sizes...immediately available through leading surgical/hospital suppliers.

For clinical references and technical data, request C. R. Bard catalog supplements Teflon 3-R and Dacron 10

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1. Selzer, A., and Rytand, D. A.: COUNCIL ON DRUGS, Report to the Council, J.A.M.A. 168:762 (Oct. 11) 1958.

2. Weil, M. H.: J.A.M.A. 171:1868, (Nov. 28) 1959.

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Fast-acting Milprem directly relieves both emotional dread and estrogen deficiency

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Radiograph on Kodak Blue Brand X-ray Film;
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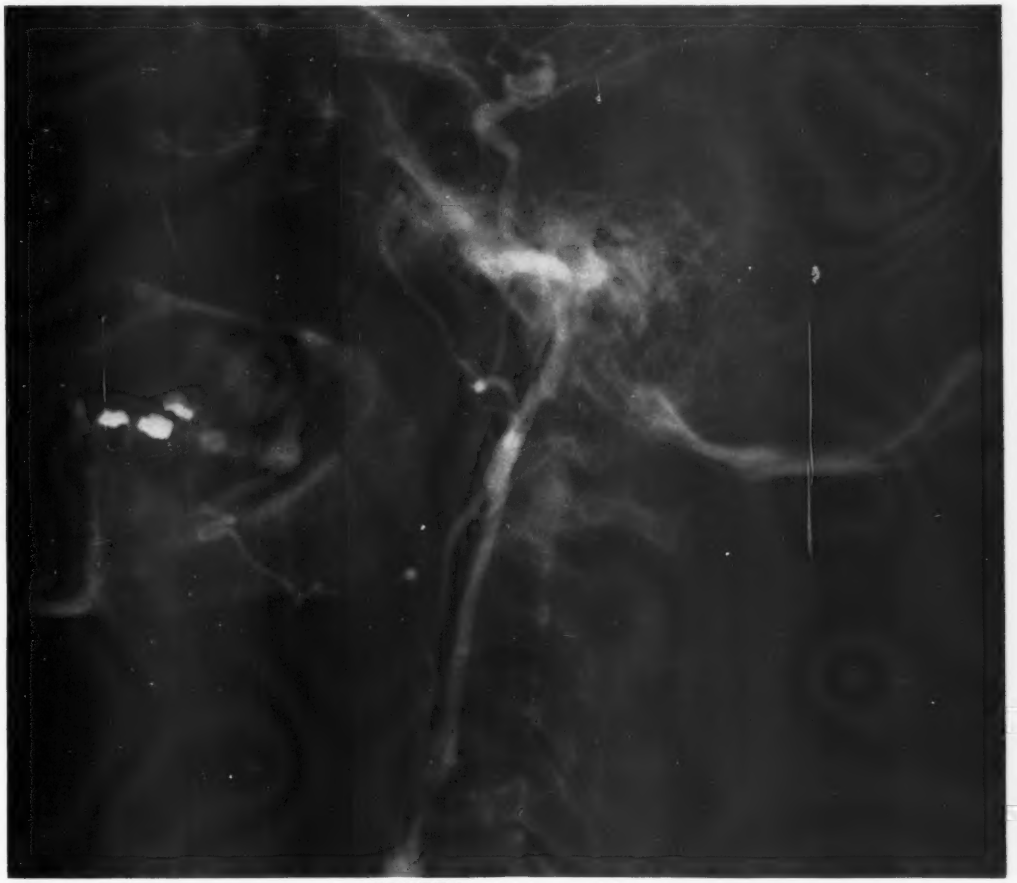

FIGURE 1.

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FIGURE 2.

Figure 1: Preoperative carotid arteriogram shows carotid arteries with sclerotic narrowing of the internal carotid artery at its origin. **Figure 2:** Incision along anterior border of the sternocleidomastoid muscle.

CAROTID ARTERIAL INSUFFICIENCY— *SURGICAL CORRECTION* (cont'd)

FIGURE 3.

FIGURE 4.

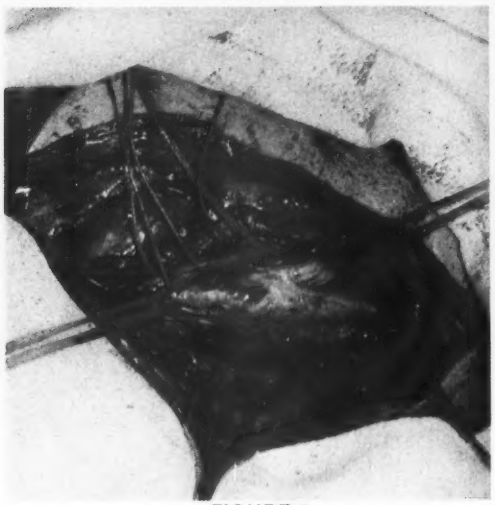

FIGURE 5.

FIGURE 6.

Figure 3: Retraction of sternocleidomastoid muscle exposes deep cervical fascia. (Parotid gland now visible at upper pole of incision.) **Figure 4:** Tapes in place about internal jugular vein. **Figure 5:** Tapes around the carotid arteries. **Figure 6:** Internal carotid artery open and arteriosclerotic "core" being removed. *Note how effectively color establishes tissue differentiations.*

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FEB. 1961 (P-546)

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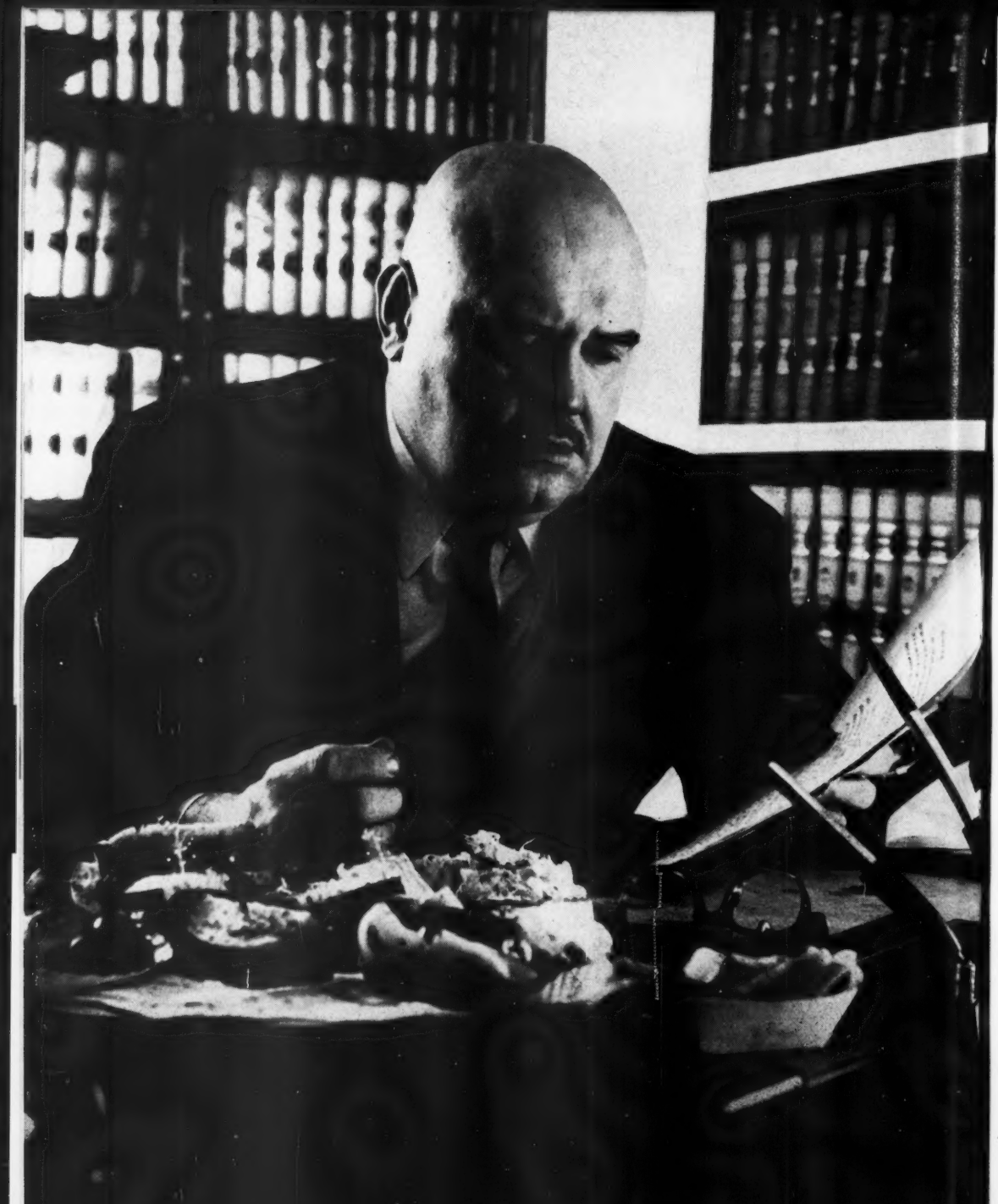
REFERENCES: (1) Coon, W. W.; Wolfman, E. E., Jr.; Foote, J. A., & Hodgson, P. E.: Am. J. Surg. *98:1, 1959. (2) Friedman, E. A.; Little, W. A., & Sachtleben, M. R.:* Am. J. Obst. & Gynec. *79:474, 1960. (3) Margulis, R. R., & Brush, B. E.:* Arch. Surg. *65:511, 1952. (4) Personal Communications to the Department of Clinical Investigation, Parke, Davis & Company, 1959.*



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SPECIAL PROBLEM: EDEMA

Since it does not produce edema, triamcinolone is useful in rheumatoid arthritis patients with cardiac decompensation who need steroid therapy. (Hollander, J. L.: *J.A.M.A.* 172:306 [Jan. 23] 1960.)

SPECIAL PROBLEM: HYPERTENSION

Triamcinolone may be included among the currently available antirheumatic steroids having the least tendency to cause sodium retention. (Ward, L. E.: *J.A.M.A.* 170:1318 [July 11] 1959.)

Hypertension did not result from triamcinolone therapy. Existing hypertension was reduced sometimes. This may have been due to lack of sodium retention. (Freyberg, R. H.; Berntsen, C. A., Jr., and Hellman, L.: *Arthritis & Rheumatism* 1:215 [June] 1958.)

Precautions: Collateral hormonal effects generally associated with corticosteroids may be induced. These include Cushingoid manifestations and muscle weakness. However, sodium and potassium retention, edema, weight gain, psychic aberration and hypertension are exceedingly rare. In the treatment of rheumatoid arthritis, dosage should be individualized and kept at the lowest level needed to control symptoms. Dosage should not exceed 36 mg. daily without potassium supplementation. Drug should not be withdrawn abruptly. Contraindicated in herpes simplex and chicken pox.

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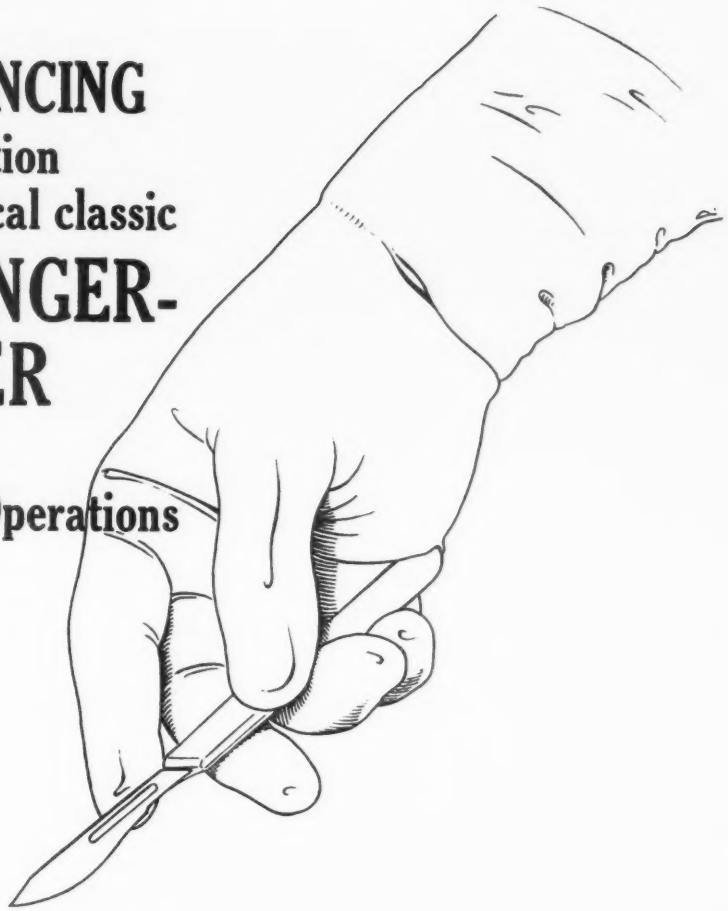

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A SERIOUS AND GROWING PROBLEM: An increasing number of reports[1-18] attest to the rising frequency of life-threatening infections due to Gram-negative organisms that are resistant to the commonly used antibiotics. Such infections have become almost as serious a clinical problem as those caused by resistant staphylococci. They assume critical importance in patients with low resistance and in patients compromised by debilitating illness.

HOW KANTREX (INTRAMUSCULAR) MEETS THE PROBLEM: Kantrex is effective against many strains of Gram-negative pathogens that are resistant to the commonly used antibiotics.[4,6,14-17] Kantrex is bactericidal, not merely bacteriostatic. It is rapidly absorbed after intramuscular injection, reaching peak blood levels in about one hour, and remains in most patients, in the active range for sensitive pathogens for 8 to 12 hours. Because Kantrex is bactericidal, it often produces a dramatic effect even in patients with lowered resistance. Of the few special-use antibiotics that have been found effective in combating resistant Gram-negative infections, Kantrex has the broadest history of clinical application.

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CURRENT PLACE OF KANTREX AGAINST RESISTANT STAPHYLOCOCCI AND ENTEROCOCCI: In resistant staphylococcic infections, if for some reason Staphcillin may not be used, Kantrex should be considered among other antibiotics. In mixed infections due to strains of resistant staphylococci and Gram-negative organisms, both of which are sensitive to kanamycin, Kantrex may be a preferred antibiotic. Kantrex is also indicated in the treatment of some resistant enterococcic infections due to strains shown to be sensitive to kanamycin.

INDICATIONS: Kantrex is indicated in the treatment of Gram-negative, staphylococcic and enterococcic infections due to organisms shown to be sensitive to kanamycin, including strains resistant to other antibiotics. These infections include septicemia, postoperative wound infection, soft tissue infection, peritonitis, and pulmonary infection. Kantrex is of particular value in urinary tract infections due to Gram-negative organisms resistant to other antibiotics. Especially serious is a long-standing pyelonephritis in a debilitated patient, for such infections constitute the most common source of Gram-negative bacteremias[7,11,16] which may become life-threatening.

PRECAUTION: The major toxic effect of parenterally administered kanamycin is its action on the auditory portion of the eighth nerve. To minimize the risk of ototoxicity, the daily dose of 15 mg./kg. should not be exceeded nor should the duration of therapy be prolonged. The drug should be used with caution in reduced dosage in patients with impaired renal function to avoid excessively high blood levels. Evidence of renal irritation frequently occurs during therapy, but this effect appears to be reversible on cessation of therapy and is not necessarily an indication for withdrawing the drug if the patient's infection is responding.

There have been no reports of blood dyscrasias or other hematologic disorders, no liver toxicity.

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SUPPLY: Kantrex Injection, 0.5 Gm. kanamycin (as sulfate) in vial containing 2 ml. volume; and 1.0 Gm. in vial containing 3 ml. volume.

REFERENCES: 1. Finland, M.: *New England J. Med. 263*:207 (Aug. 4) 1960. 2. Cutts, M.: *Rhode Island M. J. 43*:388 (June) 1960. 3. Hannigan, C. A., *et al.: J. Maine M. A. 51*:77 (March) 1960. 4. Griffith, L. J., *et al.: Antibiotics & Chemother. 10*:88 (Feb.) 1960. 5. Editorial: *New England J. Med. 261*:1081 (Nov. 19) 1959. 6. Bernard, L. A. and Sutton, W. C.: *A.M.A. Arch. Int. Med. 105*:311 (Feb.) 1960. 7. Kirby, W. M. M. *et al.: J.A.M.A. 162*:1 (Sept.) 1956. 8. Bryer, M. S.: *Am. J. Med. 18*:782 (May) 1955. 9. Editorial: *New England J. Med. 262*:578 (Mar. 17) 1960. 10. Rogers, D. E.: *New England J. Med. 261*:677 (Oct. 1) 1959. 11. Holloway, W. J. and Scott, E. G.: *Delaware M. J. 32*:314 (Aug.) 1960. 12. Finland, M. *et al.: J.A.M.A. 170*:2188 (Aug. 29) 1959. 13. Schneierson, S. S.: *New York J. Med. 60*:3426 (Nov. 1) 1960. 14. Lattimer, J. K. *et al.: J.A.M.A. 170*:938 (June 20) 1960. 15. Holloway, W. J. *et al.: Delaware M. J. 32*:49 (Feb.) 1960. 16. Bunn, P. A. and Baltch, A.: *New England J. Med. 259*:659 (Oct. 2) 1958. 17. Koota, G. M. *et al.: New England J. Med. 263*:629 (Sept. 29) 1960. 18. Finegold, S. M.: *A.M.A. Arch. Int. Med. 104*:15 (July) 1959.

NOTE: Kantrex is also available in the form of capsules for local effect in gastrointestinal-tract infections, for preoperative bowel sterilization, and for adjunctive treatment in certain hepatic comas. The Capsule form is *not* intended for use in the treatment of systemic infections. See Official Package Circular for complete details.

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	K. pneumoniae	•	•		
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	Pseudomonas	•	•		
	Brucella		•		
	Salmonella	•	•		
	Shigella	•	•		
Rickettsia	R. akari		•		
	R. prowazekii		•		
	R. typhi		•		
	R. rickettsii		•		
	R. tsutsugamushi		•		
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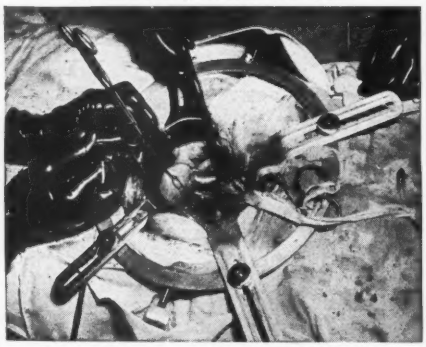

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Britton, Richard C.: Management of Peripheral Edema, Including Lymphedema of the Arm After Radical Mastectomy, Cleveland Clinic Quarterly, Vol. 26: No. 2, pp. 53-61, April, 1959.

Brush, Brock E.; Wylie, John H.; and Beninson, Joseph: Some Devices for the Management of Lymphedema of the Extremities, The Surgical Clinics of North America, Vol. 39: No. 6, pp. 1493-1498, December, 1959.

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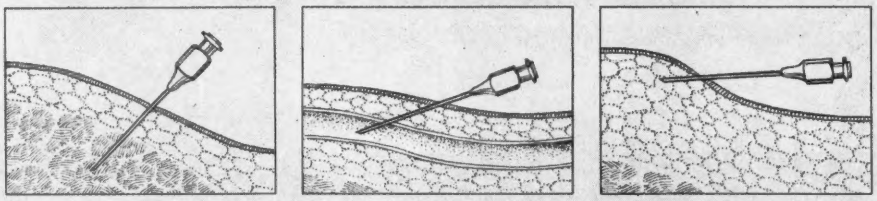

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*Council on Drugs: New and Nonofficial Drugs, Philadelphia, J. B. Lippincott Co., 1960, p. 732

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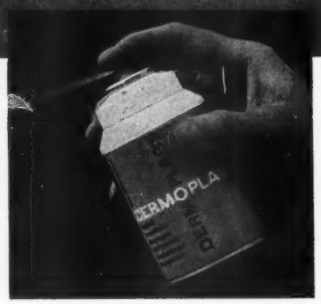

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1. Coolidge, C. W.; Glisson, C. S., Jr., and Smith, A. A.: J. M. A. Georgia 48:167 (Apr.) 1959. 2. Ensey, J. E.: Am. J. Obst. & Gynec. 77:155 (Jan.) 1959. 3. Frech, H. C., and Lanier, L. R., Jr.: J. M. A. Georgia 47:498 (Oct.) 1958.

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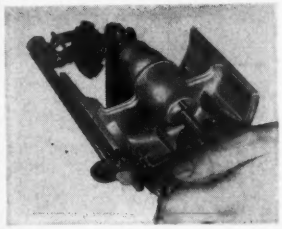

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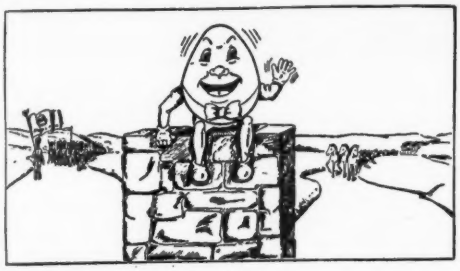

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References: (1) Kuntze, C. D.: J. Mississippi M. A. *1*:643-644 (Dec.) 1960. (2) Napp, E. E., and Donnenfeld, A. M.: J. Am. Geriatrics Soc. *8*:858-860 (Nov.) 1960. (3) Lamphier, T. A., and Lyman, F. L.: J. Internat. Coll. Surgeons *31*:420-423 (April) 1959.

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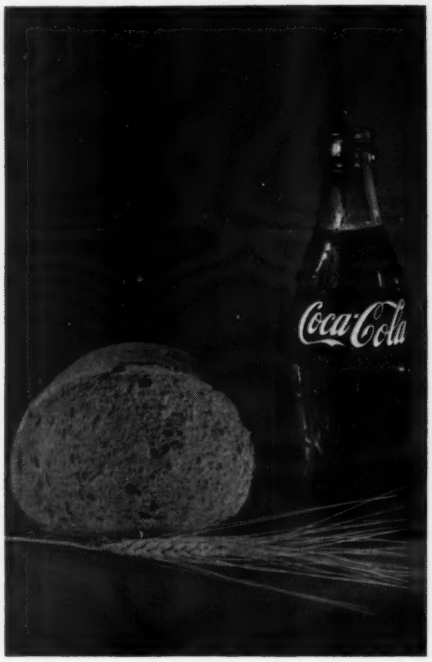

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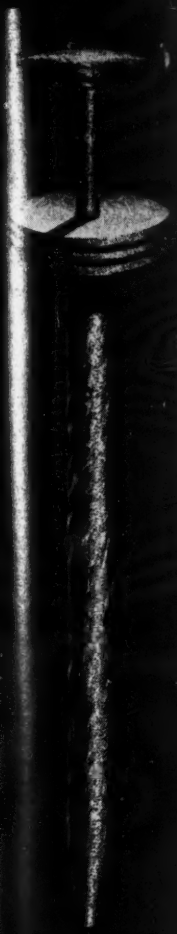

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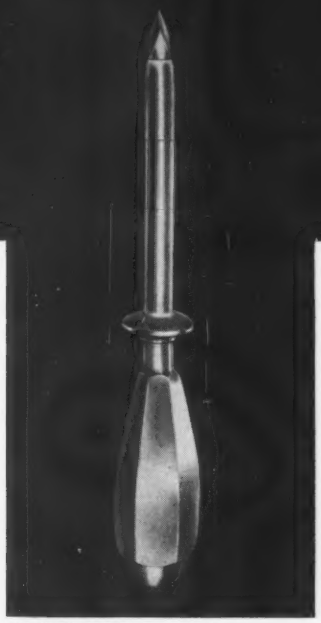

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DOSAGE: One or two capsules four times a day. See Official Package Circular for complete information on dosage, side effects and precautions.

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REFERENCE: 1. Rhoads, P. S.: *Postgrad. Med. 21*:563 (June) 1957.

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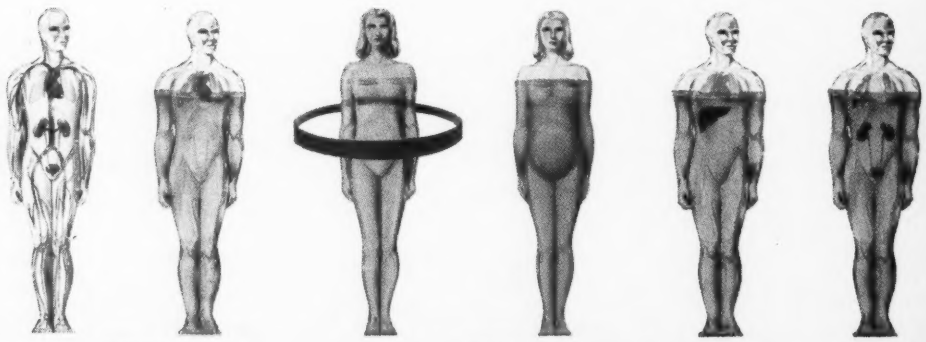

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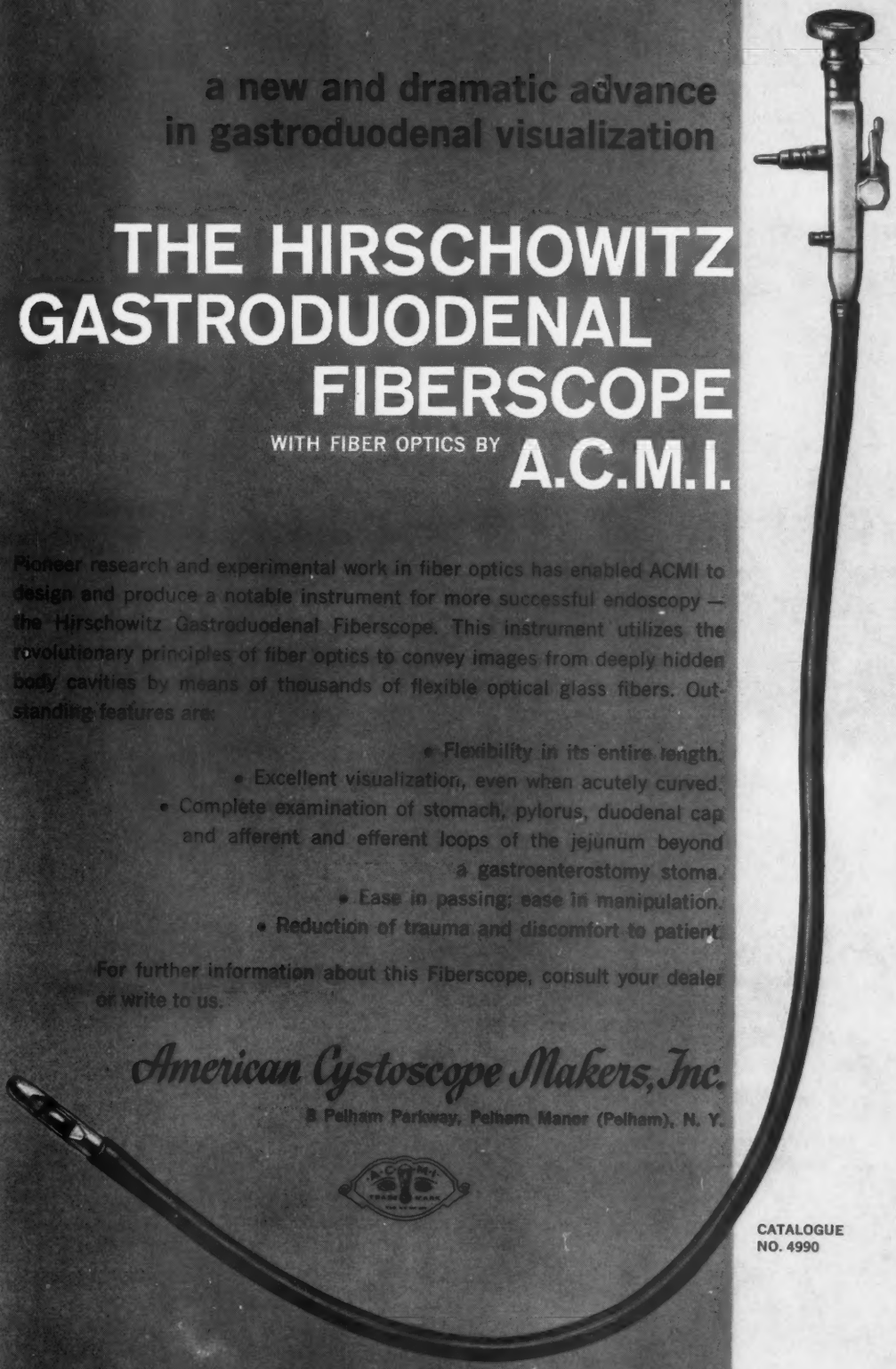

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VISTARIL prepartum . . .
allays apprehension and fear without impairing ability to cooperate during labor and delivery[1]

reduces narcotic requirements and incidence of narcotic-induced respiratory depression; helps control nausea and vomiting; shortens stay in recovery room[1,2]

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References: 1. Benson, C., and Benson, R. C.: Scientific Exhibit, Illinois Acad. Gen. Practice, Sept., 1960.
2. Grady, R. W., and Rich, A. L.: Scientific Exhibit, Am. Soc. Anesth., New York, Oct. 4-7, 1960.

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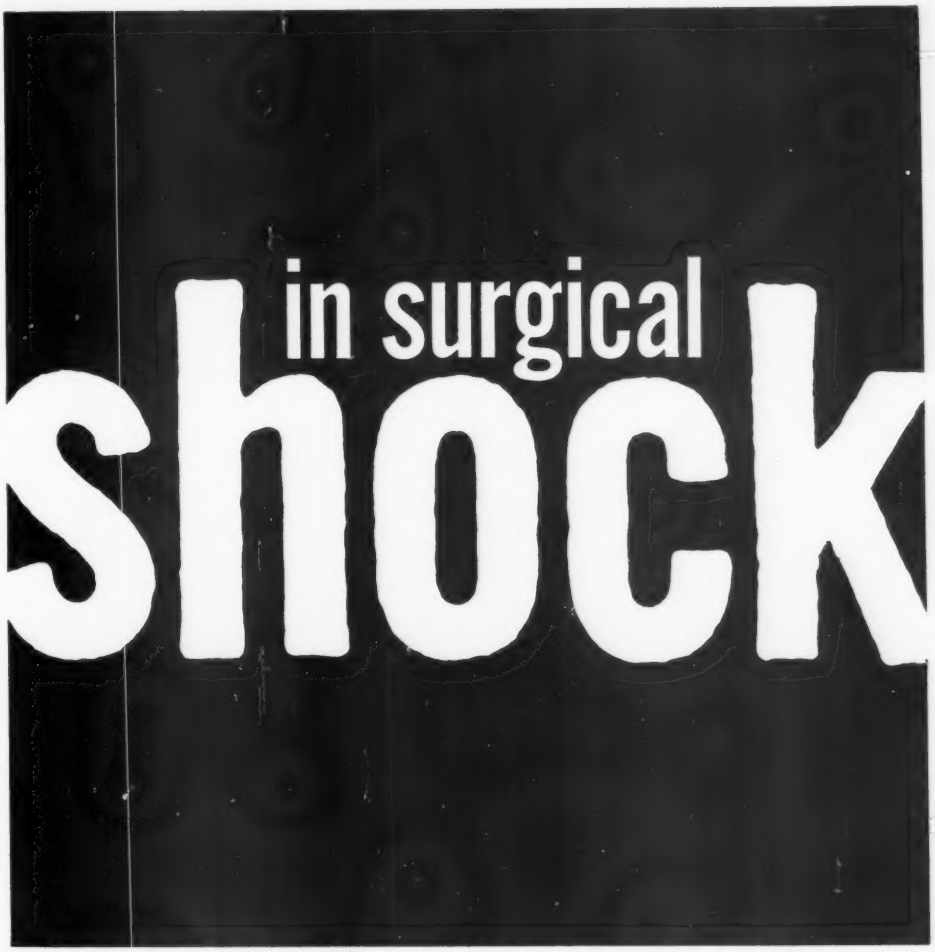

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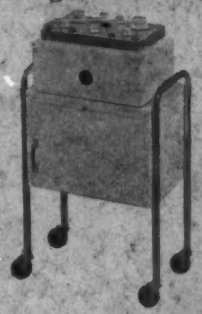

The Birtcher BLENDTOME electrosurgical unit offers all four technics: electrosurgical cutting, fulguration, desiccation and coagulation.

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